FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS BY USING CENTRAL COMPOSITE DESIGN FOR ANTI HYPERTENSIVE DRUG LOSARTAN POTASSIUM

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted By

Amarnadh Ambedkar Y

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DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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Under the guidance of

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CERTIFICATE

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Place: Nagapattinam

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LIST OF ABBREVIATION

ABBREVEATIONS	FULL-FORMS
#	Mesh
% CDR	% Cumulative Percent Drug Released
% w/v	Percentage weight by volume
% w/w	Percentage weight by weight
^{0}C	Temperature on Celsius Scale
Abs	Absorbance
BP	British Pharmacopoeia
Cm	Centimeter
Cm^2	Centimeter Square
DCP	Dicalcium Phosphate Anhydrous
DSC	Differential scanning calorimetry
CR	Controlled release
FD&C	Food Drug and Cosmetic
Fig.	Figure
EC	Ethyl Cellulose
Gm	Grams
HPMC K4M	Hydroxypropyl Methyl Cellulose K4M
H	Hours
ICH	International Conference on harmonization
IP	Indian Pharmacopoeia
IR	Infrared
Kg/cm^2	Kilogram per centimeter square
L	Liter
Mg	Milligram
Mm	Millimeter

Ng	Nanogram
Nm	Nanometer
R	Regression Coefficient
Rpm	Revolutions per minute
SD	Standard Deviation
λmax	Absorption maxima
USP	United States Pharmacopoeia
UV	Ultraviolet
w/w	Weight by weight
Wt.	Weight
µg/ml	Microgram

ABSTRACT

The central composite design was used to develop the controlled release buccoadhesive tablets containing losartan potassium. Locust bean gum and hydroxy propyl methylcellulose K4M (HPMC K4M) were taken as factors. Bioadhesive strength, drug release at 1 h, drug release at 8 h, release exponent (n) and hardness were taken as responses. The polymers had shown significant effect for all response. A backing layer of ethyl cellulose was used which is impermeable in nature. Nine different

formulations of losartan potassium were prepared by direct compression method. The preformulation study using FTIR spectroscopy and DSC revealed the compatibility of drug and polymer. The prepared tablets were characterized by swelling studies, surface pH, bioadhesive properties and *In-vitro* drug dissolution. All the formulations gave the satisfactory results. It was found that locust bean gum gives higher bioadhesive strength than HPMC K4M. Both the polymers given satisfactory swelling effect. The surface pH of all formulations was found to be satisfactory, and values of pH were in between the range of 5-7, hence no irritation to buccal cavity is assumed. All the tablets showed *ex vivo* residence time of 7.2 h to >10 h indicated good adhesive capacity of tablet. The optimized formulation follows Fickian diffusion release mechanism. Stability study was carried out for optimized formulation as per ICH guidelines and no major change was observed.

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1. INTRODUCTION

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as carriers. Amongst various routes of drug delivery oral route is perhaps the most preferred to the patient and the clinician alike. However this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug in some cases can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs[1].

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route [2].

The thin mucin film, which exists on the surface of the oral mucosa may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged

periods if it is designed to be mucoadhesive. Such system ensures a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. Therefore, the oral mucosa may be a potential site for controlled or sustained drug delivery. In this respect, the buccal and gingival areas are associated with a smaller flow of saliva, as compared to the sublingual region, thus the duration of adhesion of the delivery system would be longer at these areas than at the sublingual region[3].

Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides as well as conventional small drug molecules. The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides[4].

Cardiovascular diseases account for a large proportion of all deaths and disability worldwide. Global Burden of Disease (GBD) Study reported that there were 5.2 million deaths from cardiovascular diseases in economically developed countries and 9.1 million deaths from the same causes in developing countries. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Pooling of Indian epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects. Therefore cost effective approaches to optimally control

blood pressure among Indians are very much needed. Although novel drug-delivery systems have been used in other areas of medicine, their application in the treatment of hypertension has been relatively recent[5].

1.1 Drug delivery via buccal route:

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

Avantages of Buccal Drug Delivery Systems[4,6]:

Drug administration via buccal mucosa offers several distinct advantages,

1. Ease of administration.

2. Permits localization of the drug in the oral cavity for a prolonged period of time.

3. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.

4. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.

5. Drugs which are unstable in acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine.

6. The presence of saliva ensures relatively large amount of water for drug dissolution unlike the case of rectal and transdermal routes.

7. It offers passive system for drug absorption and does not require any activation.

8. It can be made unidirectional to ensure only buccal absorption.

9. The buccal mucosa is highly perfused with blood vessels and offers greater permeability than the skin.

10. Therapeutic serum concentrations of the drug can be achieved more rapidly.

11. Better patient compliance than vaginal, rectal and nasal route of administration.

12. Buccal mucosa is less prone to damage or irritation than nasal mucosa and shows short recovery times after stress or damage.

13. Termination of therapy is easy.

14. Can be administered to unconscious patients.

15. Increased patient's compliance.

Disadvantages of buccal drug delivery system[4,6]:

Drug administration via buccal mucosa has certain limitations,

1. Drugs which irritate the oral mucosa have a bitter or unpleasant taste or odour cannot be administered by this route.

2. Drugs, which are unstable at buccal pH, cannot be administered by this route.

3. Only drugs with small dose requirements can be administered.

4. Drugs may get swallowed with saliva and loses the advantages of buccal route.

5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.

6. Over hydration may lead to the formation of slippery surface and structural integrity of

the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

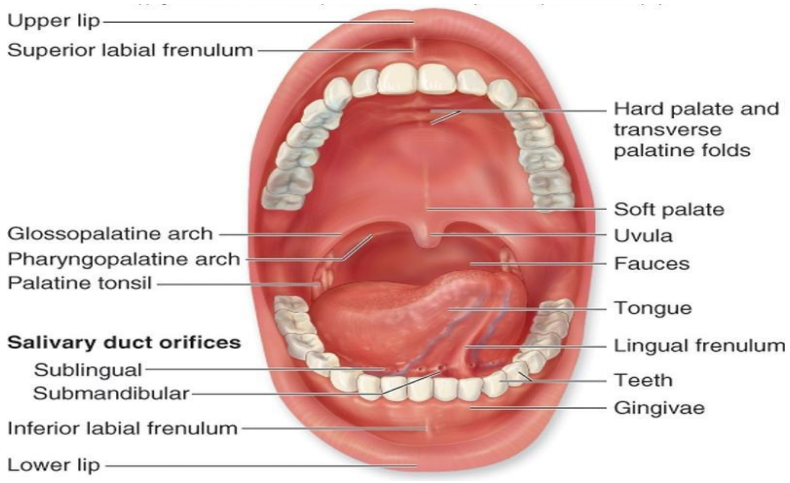
7. Surface area available for absorption is less.

8. The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

1.2 Anatomy and Nature of Oral Cavity:

1.2.1 Oral Cavity[7]:

Oral cavity is the foremost part of digestive system of human body due to its excellent accessibility and reasonable patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and syste mic therapy.



1.2.2 Overview of oral cavity:

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

1. Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).

2. Oral cavity proper, which extends from teeth and gums back to the faces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue

projects from the floor of the cavity.

The drug administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein[8]. The secretion in the oral cavity includes saliva, crevicular fluid and mucus. From that, Saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time, glands had been stimulated, the age and sex of the individual and by their state of health. The average resting flow rate for whole saliva is 0.3 ml/min (range 0.1-0.5 ml/min). For stimulated saliva the average flow rate is 1.7ml/min (range 1.1 to 3.0 ml/min). Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes[9].

1.3 Oral Mucosa:

1.3.1 Anatomy and physiology of the oral mucosa:

The mucosa that lines the oral cavity may be divided into three types, classified according to their function as;

1. Masticatory mucosa: Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.

2. Lining mucosa: Which covers the lips, cheeks, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non-keratinized epithelium.

3. Specialized mucosa: covering the dorsum of the tongue with highly keratinization. Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is in turn supported by connective tissues (Fig 2). The epithelial cells originating from the basal cells mature change their shape and increase in size while moving towards the surface. The thickness of buccal epithelium in humans, dogs and rabbits has been determined to be approximately 500–800 μm. The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues and functions as a mechanical support for the epithelium.

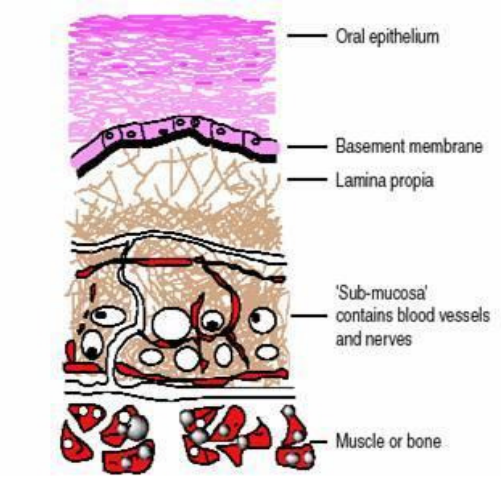


Figure 2: Structure of buccal mucosa

1.3.2 Mechanisms involved in drug absorption across the oral mucosa:

The mechanisms by which drugs cross biological lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Small water-soluble molecules may pass through, small water filled pores. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of high concentration in the mouth to a region of low concentration within the buccal tissues. Further diffusion then takes place into the venous capillary system, with the drug eventually reaching the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for this diffusion process. The permeability barrier property of the oral mucosa is predominantly due to intercellular materials derived from the so-called, membrane coating granules (MCGs). MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. These organelles have also been referred to as small spherically

shaped granules “corpusula”, small dense granules, small lamellated bodies, lamellated dense bodies, keratinosomes, transitory dense bodies and cementsomes. MCGs are found near the upper, distal or superficial border of the cells and a few occur near the opposite border. Several hypotheses have been suggested to describe the functions of MCGs including a membrane thickening effect, cell adhesion, production of a cell surface coat, cell desquamation and permeability barrier. They discharge their contents into the

intercellular space to ensure epithelial cohesion in the superficial layers and this discharge forms a barrier to the permeability of various compounds[1]

1.4. TYPES OF BUCCAL DRUG DELIVERY SYSTEM[12, 6]:

For delivery of drug through buccal region several mucoadhesive dosage forms have been reported because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage forms the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a mucoadhesive system. The various types of buccal drug delivery system are explained as follows;

1. Buccal Tablets
2. Buccal Patches and Films
3. Buccal Semisolids (ointments and gels)
4. Buccal Powders

1. BUCCAL TABLETS

- Adhesive tablets are held between the gum and cheek.
- Generally flat, elliptical or capsule-shaped.
- Troches & lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat.
- Buccoadhesive tablet may be monolithic or bilaminated system.
- Monolithic is multidirectional release.
- Bilayered containing core layer & backing layer.
- Backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated caster oil or may be polymeric coating layer.
- Backing layer avoids sticking of the tablet to the finger during application.

LIMITATIONS OF BUCCAL TABLETS

- The small surface of contact with mucosa.

- Their lack of physical flexibility.
- It is difficult to get high release rate, which is required for some drugs.
- The extent and frequency of contact may cause irritation following chronic application of the buccal mucosa.

2. BUCCAL PATCHES AND FILMS

Buccal patches consists of two ply laminates or multilayered thin film round or oval as consisting of basically of bioadhesivc polymeric layer and impermeable backing layer to provide unidirectional flow of drug across buccal mucosa. Buccal bioadhcsivc films are formulated by incorporating the drug in alcohol solution of bioadhesive polymer.

Example:

- Isosorbid dinitrate in the form of unidirectional errodible buccal film are developed and characterised for improving bioavailability.
- Buccal film of salbutamol sulphate and terbutalin sulphate for the treatment of asthma.
- Buccoadhesive film of clindamycin used for pyorrhoea treatment.

3. BUCCAL SEMISOLID DOSAGE FORMS

A buccal semisolid dosage form consists of finally powdered natural or synthetic polymer dispersed in a polyethylene or in aqueous solution. Example: Gels, Ointments, orabase

- Gels are usually clear, transparent, semisolids containing solubilized active substances. Forming hydrophilic polymers is typically used to prepare lipid-free semisolid dosage forms.
  E.g: Methylcellulose, carbopols, hydroxyl ethylcellulose etc.
- Vehicles containing therapeutic agents are especially useful for application to mucus membranes and ulcerated or burned tissues, because their high water content reduces irritancy.
- Due to plastic rheological behaviour they can remain to the surface of application for a reasonable duration before they are washed off.

- In comparison to solutions, gels can significantly prolong residence time and hence improve bioavailability. Eg. Glibenclamide
- One of the original oral mucosal-adhesive delivery systems- "orabase" consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.

4. BUCCAL POWDER DOSAGE FORMS

Buccal bioadhesive powder dosage forms are a mixture of bioadhesivc polymers and the drug and are sprayed onto the buccal mucosa.

1.5. Conventional Dosage Form [13]:

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges (pastilles or cough drops) are usually made with the drug incorporated in a flavoured, hard-candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy–moulding process. Troches, on the other hand, are manufactured by compression as are other tablets. These two classes of tablets are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps minute or less.

1.6. MUCOADHESSION/BIOADHESION[14]: -

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces

amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. These systems have been used since long time in the development of products for various biomedical applications.

1.6.1. Theories of bioadhesion/mucoadhesion:

The mechanism ob bioadhesion follows complex formation. There are six theories that explain the detailed theory of mucoadhesion or bioadhesion. Bioadhesion take place between a biological substance and with a synthetic or natural polymer. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion. The theories include,

a. Electronic theory

b. Wetting theory

c. Adsorption theory

d. Diffusion theory

e. Mechanical theory

f. Cohesive theory

a) Electronic theory

This theory is based on the assumption that the bioadhesive material and the glycoprotein mucin network have different electronic structures. When the two materials come in contact with each other electron transfer will occur causing the formation of a double layer of electrical charge at the interface. The bioadhesive force is due to attractive forces across this electrical double layer. The system is charged when the adhesive and the substrate are in contact and discharged when they are separated. However, this theory has

caused some controversy regarding whether the electrostatic forces are an important cause or the result of the contact between the bioadhesive and the biological tissue.

b) Wetting theory

The wetting theory was based upon prediction of the intimate contact between the mucoadhesive polymer and the mucous leading to dispelling of barrier substances, spreading, and subsequent adhesion, in liquid state, utilizing interfacial tension. This theory involves calculation of the contact angle and the thermodynamic work of adhesion; and the work done related to the surfacetension of both the adhesive and the substrate, calculated with the Dupre's equation (Pritchard WH. 1970), the horizontal resolution of the forces with the Young equation, and the spreading coefficient (*Sb*).

Dupre's equation: $\omega A = \gamma b + \gamma \tau - \gamma bt$

Young equation: $\gamma ta = \gamma bt + \gamma baCOS\theta$

Spreading coefficient: $Sb = \gamma ta - \gamma bt - \gamma ba$

Where ωA was the specific thermodynamic work of adhesion and γb represents the surface tensions of the bioadhesive polymer, $\gamma \tau$ represents the surface tension of the substrate, γbt represent the interfacial tension between the tissue and polymer, θ represent the angle of contact, γba represent the interfacial tension between polymer and air, and γta represent the interfacial tension between tissue and air. Young equation state that wetting will be complete if θ will approach zero, that was the vector γta greatly exceeds $\gamma bt + \gamma ba$; while a θ vale greater than zero will result in incomplete wetting. In order to achieve adhesion of mucoadhesives to a biological membrane spreading coefficient should be positiv that is bioadhesion is favoured by large values of γta or by small values of γbt and γba

c) Adsorption theory

According to adsorption theory mucoadhesion results from secondary molecular interactions like electrostatic attraction, hydrophobic interactions, hydrogen bonds, van der Waals forces, or other related forces; associated with re-orientation of polar molecules or groups at the interface or with chemisorptions

d) Diffusion theory

The diffusion theory states that interpenetration of the chains of polymer and mucin to a sufficient depth results from the existing concentration gradients and consequential interpenetration; until an equilibrium penetration depth was achieved, in the range of 0.2 to 0.5 μm; creates a semi-permanent bond through entanglement and mechanical interlocking between mucin and mucoadhesives. The mean diffusional depth (*S*) of the bioadhesive polymer segments can be calculated from contact time (*t*) and diffusioncoefficient value (*D*) with the following relation.

$$S = (2tD).$$

But the time to bioadhesion of a particular polymezr (*t*) can be calculated from the diffusion coefficient of a bioadhesive through the substrate value (*Db*) and the interpenetrating depth (*l*), with the following relation.

$$t = l2/Db$$

e) Fracture theory

The fracture theory was based on analysis othe force required for the separation of two surfaces after adhesion using tensile apparatus employing following relation that relates fracture strength (σ), fracture energy (ϵ), young modulus of elasticity (E) and critical crack length (L). $\sigma = (E \times \epsilon/L)$.

1.6.2. Factors affecting mucoadhesion in the oral cavity[15,11]:-

Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. A variety of factors affect the mucoadhesive properties of polymers, such as molecular weight, flexibility, hydrogen bonding capacity, cross-linking density, charge, concentration, and hydration (swelling) of a polymer, which are briefly addressed below.

Polymer-related factors

1.6.2.1. Molecular weight.

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000.

1.6.2.2. Flexibility.

Bioadhesion starts with the dif- fusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. A recent publication demonstrated the use of tethered poly (ethylene glycol), poly (acrylic acid) hydrogels and their copolymers with improved mucoadhesive properties. The increased chain interpenetration was attributed to the increased struc-tural flexibility of the polymer upon incorporation of poly (ethylene glycol). In general, mobility and flexi-bility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucusnetwork .

1.6.2.3. Hydrogen bonding capacity.

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have

functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, are polymers with good hydrogen bonding capacity.

1.6.2.4. Cross-linking density.

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer net-work occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

1.6.2.5. Charge.

Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. It has been shown that some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high molecular weight polymers, such as chitosan, have shown to possess good adhesive properties.

1.6.2.6. Concentration.

The importance of this factor lies in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an unperturbed state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties. One of the studies addressing this factor demonstrated that high concentrations of flexible polymeric films based on polyvinylpyrrolidone or poly (vinyl alcohol) as film-forming polymers did not further enhance the mucoadhesive properties of the polymer. On the contrary, it decreased the desired strength of mucoadhesion.

1.6.2.7. Hydration (swelling).

Hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs.

1.6.2.8. Environmental factors

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on both the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5. The pH of the microenvironment surrounding the mucoadhesive polymer can alter the ionization state and, therefore, the adhesion properties of a polymer. Mucin turnover rate is another environmental factor. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12–24 h in humans. Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within the oral cavity continue even during sleep, and can potentially lead to the detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors.

Ideal drug candidates for buccal drug delivery System[16]

- The conventional single dose of drug should be low.
- Through oral route, the drug may exhibit first pass effect or presystemic drug elimination.
- The drug should not adversely affect the natural microbial flora or oral cavity.
- Drug should not have bad taste and be free from irritancy, allergenicity and discoloration or erosion of teeth.

Marketed products[17]

Buccal mucosa formulations

Buccastem- manufactured by reckitt and colman in United Kingdom.

Suscard Buccal- manufactured by Pharmax.

1.7. Mucoadhesive polymers used in the oral cavity[18,11]:

1.7.1. Desired characteristics:

The polymer-related factors have been briefly discussed in the previous section. Generally, some of the necessary structural characteristics for bioadhesive polymers include strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility, and surface energy properties favoring spreading on a mucus layer.

1.7.2. Classification:

In general, adhesive polymers can be classified as synthetic vs. natural, water soluble vs. water insoluble, and charged vs. uncharged polymers. Examples of the recent polymers classified in these categories are listed in Table. Natural bioadhesive macromolecules share similar structural properties with the synthetic polymers. They are generally linear.

Criteria	Categories	Examples
Source	Semi-atural/natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate, locust bean gum).
	Synthetic	Sodium CMC, HEC, HPC,

		HPMC, Carbopol etc.
Aqueous solubility	Water-soluble	CP, HEC, HPC, HPMC, PAA, sodium CMC, sodium alginate
	Water-nsoluble	Chitosan, EC, PC
Charge	Cationic	Aminodextran, chitosan, trimethylated Chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum.
	Non-ionic	Hydroxyethyl starch, HPC, PVA, PVP
Forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates, CP, PVA
	Electrostatic Interaction	Chitosan

Table 1: Classification of mucoadhesive polymers in buccal drug delivery

1.7.3. CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER:

1. Rapid adherence to mucosa.

2. Exhibit strong interaction with the mucin epithelial tissue.

3. Minimum impact on drug release.

4. Good spreadability, wetting, swelling and solubility and biodegradability properties.

5. Unaffected by the hydrodynamic conditions, food and pH changes.

6. Easy to incorporate in various dosage forms.

7. Possess peel, tensile and shear strengths at the bioadhesive range.

8. Show bioadhesive properties in both dry and liquid state.

9. Demonstrate local enzyme inhibition and penetration enhancement properties.

10. Demonstrate acceptable shelf life.

11. Optimum molecular weight.

12. Possess adhesively active groups.

13. Possess required spatial conformation.

14. Sufficiently cross-linked but not to the degree of suppression of bond forming groups.

15. Possess good viscoelastic properties and no breakdown at the mucosa.

1.8. OPTIMIZATION1[19]

The word optimize is defined as, to make as perfect, effective or functional as possible. Optimization may be interpreted as to find out the values of controllable independent variables, that gives the most desired value of dependent variables. In the trial and error method, a lot of formulations have to be prepared to get a conclusion, which involves lot of money, time and energy. These can be minimized by the use of optimization technique.

1.8.1. Optimization process:

Generally optimization process involves the following steps

1. Based on the previous knowledge or experience or from literature, the independent variables are determined or set in the beginning.
2. Selection of a model based on the results of the factor screening.
3. The experiments are designed and are conducted.
4. The responses are analyzed by ANOVA, test on lack of fit, to get an empirical mathematical model for each individual response.
5. The responses are screened by using multiple criteria to get the values of independent variables.

1.8.2. Experimental design[20]

Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region, depends on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain, the point being defined by its co-ordinate (the value given to the variables) in the space.

a) Factorial design

It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs are used in experiments where the effects of different factors or conditions on experimental results are to be elucidated. These are the design of choice for simultaneous determination of the effect of several factors and their interaction.

The simplest factorial design is the two-factorial design where two factors are considered each at two levels, leads to four experiments, which are situated in 2-dimensional factor space at the corners of a rectangle. If there are three factors, each at two levels, eight experiments are necessary which are situated at the corners of an orthogonal cube in a 3-dimensional space. The number of experiments is given by 2^n, where 'n' is the number of factors.

If the number of factors and levels are large, then the number of experiments needed to complete a factorial design is large. To reduce the number of experiments, fractional factorial design can be used (i.e., ½ or ¼ of the original number of experiments with full factorial design).

The fitting of an empirical polynomial equation to the experimental result facilitates the optimization procedure. The general polynomial equation is as follows:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + \ldots + B_{12}X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3 + \ldots + B_{123}X_1X_3.$$

Where, Y is the response,

X_1, X_2, X_3 are the levels (concentration) of the 1,2,3 factors

$B_1, B_2, B_3, B_{12}, B_{13}, B_{23}, B_{123}$, are the polynomial coefficients.

B_0 is the intercept (which represents the response when the level of all factors is low).

b) Plackett – Burman design

It is a special fractional factorial design with K = m*4 experiment, for screening of (K-1) variables, Where 'K' is the number of variables and 'm' is the number of levels.

c) Star design

Star design is simply a 2^2 factorial design rotated over 45^0 angle in the space. A center point is usually added, which may be replicated to estimate the experimental error, so there will be three levels for each factor where quadratic effect can be measured, but the interaction effect cannot be measured as that in case of factorial design. In the star

designs, 2k Factorial designs are rotated over 45^0 in (k-1) direction in k-dimensional space with a replicated center point. 'k' is the number of factors in the design. This results in $2k + R_c$ experiments, where R_c is the replicates of the center point.

d) Central Composite design

A better design that combines the advantages of Factorial design or Fractional factorial design and the Star design, is the central composite design (CCD) developed by Box and Wilson. It is composed of

- 2^k Factorial design or $2^{(k-p)}$ Fractional factorial design.

- 2*k Star design, this design enables the estimation of a full second-order model. The equation for two factors is given by

$$E(y) = B_0+B_1X_1+B_2X_2+B_{12}X_1X_2+B_{11}X_1^2+B_{22}X_2^2$$

1.8.3. Validation of the model

The model is validated using ANOVA calculation, then the estimation pure measurement error is done. The variance of these observations pooled over all to get an estimate of pure error of variance. The F-test on regression and lack of fit will be useful for judging descriptive properties of a model and the significance of model terms.

1.8.4. Predictions using the selected model

Once a model is selected and validated, the brute force method is applied for the prediction of response. With the help of 3D-response surface or a 2D contour diagram, the prediction is done using these graphs either by grid search or feasibility search methods.

1.9. Software for designs and Optimization[22]

Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type.

1.9.1. Software's dedicated to experimental designs

Design Ease and Design Expert (Stat-ease)

- ECHIP
- CARD
- Multisimplex

Software for general statistical nature includes

- SAS
- MINITAB
- SYSTAT, etc.

JUSTIFICATION

For my dissertation work of formulation and evaluation of mucoadhesive buccal tablets by using central composite design for anti hypertensive drug; selected.

The main reason for the selection of losartan potassium for the formulation, it has less bioavailability (33%) due to the high first pass metabolism and it has very short half life 2.5 h and for controlled release formulation the half life should be less.

The polymer locust bean gum is a very good mucoadhesive polymer and it has a good gelling capacity. It is also controlle the drug release.

2. OBJECTIVES:

The objective of the present research work is to formulate and evaluate bilayered buccoadhesive tablet containing losartan potassium as a drug to achieve unidirectional drug release and to increase bioavailability of the drug.

The specific objectives of the present research include:

1. Locust bean gum will be selected as a primary polymer along with HPMC K4M as secondary polymer for the preparation of mucoadhesive buccal tablets.
2. To confirm the conjugation primarily by determining charring point and further by performing FT-IR and differential scanning calorimetry.
3. To formulate bilayered buccoadhesive tablet by using combination of locustbean gum along with other polymers using losartan potassium as a model drug having prolonged residence time and ethyl cellulose as an impermeable membrane.
4. To evaluate the physical characteristics like weight uniformity, thickness, hardness and drug content of the formulations.
5. To evaluate mucoadhesive characteristics like swelling index, *ex vivo* bioadhesion time and *ex vivo* bioadhesion strength.

3. REVIEW OF LITERATURE

3.1 REVIEW OF LITERATURE:

- 🕮 Reviews of literatures revealed that number of studies have been carried out on mucoadhesive buccal tablets using different techniques.
- 🕮 The drug has selected as an anti hypertensive drug in Essential medical pharmacology and the drug of the anti hypertensive is studied as its properties molecular weight, half life, bioavailability and it avoids the first pass metabolism.[22]

- 🕮 The aim of the current study was to develop the UV- spectrophotometric method for the estimation for Losartan potassium in solid pharmaceutical dosage form. The λ-max of losartan potassium was found to be 234nm to both crude and marketed sample and is analyzed using Beer-Lamberts law. The developed methods were absolute, definite, explicit and consistent and found to be a prototype for routine determination for losartan potassium. The method was validated statistically and by recovery studies. The LOD (limit of detection) and LOQ (limit of quantification) for second derivative spectra were found to be 9.7µg/ml and29.74µg/ml. The correlation coefficient value was found to be 0.9989. The purity was found to be 98%.[23]
- 🕮 The present research was losartan potassium is an angiotensin II receptor antagonist with an oral bioavailability of only 33% due to extensive first pass metabolism. Mucoadhesive buccal films of losartan potassium were prepared using hydroxypropyl methyl cellulose (HPMC) and retardant polymers ethyl cellulose or eudragit RS 100. Ex vivo permeation studies of losartan potassium solution through porcine buccal mucosa showed 90.2 % absorption at the end of 2 h. The mucoadhesive force, swelling index and tensile strength was shown higher for those formulations containing higher percentage of HPMC. Ex vivo permeation studies through porcine buccal mucosa indicate that films containing higher percentage of HPMC it showed slower permeation of the drug for 6-7 hours.[24]
- 🕮 The present work aims to investing the possibility of sustaining the Losartan potassium release from matrix tablet, prepared by hydrophilic and hydrophobic polymer. The mechanism of drug release was diffusion coupled with erosion. It can be concluded that the polymer plays a major role in the design of sustained release matrix tablet. The study reveals that the release of drug is low when the matrix tablet

contained hydrophilic and hydrophobic polymers as a combination than the other matrices and also shows anomalous (non-fickian) diffusion kinetics. Hence, it is clearly manifest the necessity of combining different classes of polymer is to get an acceptable pharmacokinetic profile in the fluctuating in vivo environment.[25]

📖 The present study was to formulate the buccal tablets of losartan potassium by using of carbopol 934P and either sodium CMC, HPMC K4M or sodium alginate in different ratios. The buccal tablets were subjected for evaluation of various physicochemical properties. In vitro drug release studies were carried out using flow thru cell. Stability studies were carried out at different conditions for two months. The results of all physicochemical parameters of all batches were satisfactory and comply with theoretically expected values. Group III formulation was shown highest percentage of drug release in In vitro release studies. Stability studies indicate no significant changes with respect to surface pH, bioadhesive strength and drug content at the end of two months.[26]

📖 The aim of the current study was to design oral controlled release matrix tablets of losartan potassium. Tablets were prepared by direct compression method by using of carbopol 934P and HPMC K 100M and evaluated for all physicochemical parameters. In vitro release studies were conducted in phosphate buffer pH 6.8 for 24 hours. The release profiles of losartan potassium from all the formulations (except F2, F3, and F8 which showed first order release) are close to zero order and follow diffusion dependent release. Irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-fickian release, the values of release exponent (n) are in between 0.584 and 0.8692.[27]

📖 The purpose of the present study was to develop a buccoadhesive drug delivery system of metoprolol tartrate (MT) using combination of natural polymers. The

tablets of MT were prepared by using semisynthetic polymer such as sodium carboxy methyl cellulose and natural polymers such as gum karaya, xanthan gum and locust bean gum. Ethyl cellulose used as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as hardness, ex vivo mucoadhesive strength, in vitro drug release and ex vivo drug permeation. Results revealed that formulation containing combination of xanthan gum and locust bean gum in 2:1 ratio exhibited complete drug release in 45 mins but poor drug permeation.[28]

📖 The present study was to develop a buccoadhesive drug delivery system of Insulin using natural polymer locust bean gum. As insulin is a peptide drug, its delivery via the buccal oral cavity has several therapeutic advantages. Locust bean gum is a mucoadhesive polymer. It is useful as a stabilizer, adsorbent and demulscent therapeutically. Mucoadhesive buccal tablets of insulin are prepared by direct compression method. Buccal tablets are evaluated by certain parameters like dissolution, in vitro bioadhesion study, drug permeation study and in vivo study. Results revealed that the tablet containing 5mg locust bean gum and 4 mg PEG, DME500 as an ideal formulation for mucoadhesive buccal delivery of insulin.[29]

📖 The current study was to design gastroretentive mucoadhesive theophylline tablets and to optimize with naturals gums and their combinations. Tablets of theophylline were prepared using direct compression method and were evaluated for different physicochemical parameters. Different types of natural gums such as locustbean gum, Carrageenan gum, natural polymer like Chitosan and synthetic polymer Carbopol were used. Out of which the formulation with the combination of locust bean gum and Chitosan (4.5:3) showed greater mucoadhesive strength, good swelling and in

vitro drug release than using a single gum, other gum combinations and synthetic polymer.[30]

- 🕮 The present study was to develop hydrophilic polymer and hydrophobic polymer based matrix Losartan potassium sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. Formulation of Losartan potassium matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. Influence of hydrophilic and hydrophobic polymer on Losartan potassium was studied. Administration of LP in a sustained release dosage would be more desirable for antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration.[31]
- 🕮 In this study, a new dosage form was developed by using carbopol 934P and hydroxypropylmethylcellulose (HPMC K4M) as bioadhesive polymers in different ratios. The mucoadhesive strength was evaluated by detachment force measurement from porcine vaginal mucosal membrane. The formulations were tested for their swelling behavior using agar gel plate. The swelling index increased with an increase in the content of HPMC. In vitro and in situ release studies were also carried out using porcine vaginal mucus membrane.[32]
- 🕮 In the present work was to develop the mucoadhesive tablet of diclofenac by using Aegle marmelos fruit gum as a binder. The preliminary evaluation of Aegle marmelos gum showed that bulk density 0.42 ± 0.2 g/cm3, tapped density 0.45 ± 0.3 g/cm3 and angle of repose 29^0 ± 0.15. The six tablet formulations were prepared by direct compression method. Tablets were subjected for evaluation of all physicochemical parameters. Formulation was studied for drug additive interaction (FTIR). F4 is found to be optimized formulation. The in-vitro drug release of F4 formulation exhibits complete release of Diclofenac Sodium with non fiction first order release kinetic.[33]

📖 The aim of study was to prepare and characterize buccoadhesive tablets of Metoprolol tartrate by using carbopol 934, sodium alginate and HPMC K4M in combination. The prepared tablets were evaluated for physicochemical parameters such as hardness, thickness, weight variation, surface pH, Ex-vivo residence time, bioadhesive strength and in vitro drug release. In vitro, bioadhesive strength and in vitro release studies showed that formulation F8 containing 1:1.25 ratio of drug and polymer combination showed optimum bioadhesive and exhibited optimum drug release (77.33±0.23).[34]

📖 The purpose of the study was to formulate and evaluate mucoadhesive bi-layer buccal tablets of propranolol hydrochloride by using the bioadhesive polymers such as sodium alginate and carbopol 971 P along with ethyl cellulose. The tablets were evaluated for all physicochemical parameters. The swelling index was proportional to sodium alginate content and inversely proportional to carbopol 971 P content. The surface pH of all tablets was found to be satisfactory, close to neutral pH; hence, no irritation would observe with these tablets. The mechanism of drug release was found to be zero-order kinetics.[35]

📖 The present study was to formulate and evaluate the bioadhesive buccal tablets of tizanidine hydrochloride. The tablets were prepared by direct compression using bioadhesive polymers such as hydroxylpropyl methylcellulose, sodium carboxymethyl cellulose alone, and a combination of these two polymers. To improve the permeation of drug, different permeation enhancers like beta-cyclodextrin hydroxypropyl beta-cyclodextrin are added to the formulations. Bioadhesion strength,

ex vivo residence time, swelling, and in vitro dissolution studies and ex vivo permeation studies were performed. In vitro release of optimized bioadhesive buccal tablet was found to be non-Fickian.[36]

- 🕮 The present work was to formulate the buccal tablets of poorly soluble drug carvedilol. Drug-Methyl-β-Cyclodextrin complex was prepared by kneading method. Dissolution rate of complex was compared with plain drug and physical mixture. The complex was incorporated into buccal tablet. The buccal tablets were evaluated for drug release, mucoadhesive strength and ex-vivo permeability. The complex showed complete release as compared to 32.8% and 42.7% from plain drug and physical mixture respectively in 60min. Thus it can be concluded that buccal tablet containing complexed CAR would have improvement in bioavailability.[37]
- 🕮 In present investigation an attempt was made to formulate and evaluate buccoadhesive tablets of Labetalol hydrochloride by using xanthan gum. Prepared buccal tablets were comparatively evaluated for the surface pH, swelling index, bio-adhesive strength, in-vivo residence time. In vitro drug release rate of Labetalol hydrochloride prepared from this material was studied in phosphate buffer of pH 6.8 containing 0.2% sodium lauryl sulphate at 37 ± 0.5^{0}c. Drug release from the tablets followed fickian diffusion.[38]
- 🕮 The present investigation concerns the development of Buccoadhesive tablets of Verapamil Hydrochloride. The Buccal tablets were formulated using four mucoadhesive polymers namely, Carbopol 934 P, HPMC K4M, Hydroxy ethyl cellulose and Sodium corboxymethylcellulose. The tablets were carried out the weight variation, content uniformity, swelling index, Bioadhesive strength and in vitro drug release. The cumulative % of drug release of formulation F6 was 97.01. In-

vitro releases of F6 was found to be diffusion controlled and followed zero order kinetics.[39]

- 🕮 The present study was to prepare the salbutamol sulphate buccal tablets by using HPMC K4M (Hydroxypropyl Methyl Cellulose) & EC (Ethyl Cellulose) in different ratios 1:1, 1:2 & 2:1. The tablets were evaluated for all physicochemical parameters. Swelling index of batches containing more HPMC K4M was greater than that of contain less HPMC K4M. In vitro bioadhesive strength studies showed that tablets containing more HPMC K4M were great bioadhesive in nature. The maximum in-vitro release observed in formulation HE1. (1:1 ratio) and the kinetics studies shows that release follows peppas model.[40]
- 🕮 The aim of the work was to formulate the buccoadhesive morphine sulphate tablets by using hydroxy propyl methyl cellulose (HPMC) with corbomer (CP).The release behavior of systems containing 30 mg of morphine sulfate and various amounts of the two polymers was found to be non-Fickian. The adhesive force was significantly affected by the mixing ratio of HPMC and CP in the tablet, and the weakest adhesion force was observed at the ratio of 1:1(HPMC: CP).[41]
- 🕮 The present study involves the formulation and evaluation of buccal tablets of glipizide. The tablets were prepared by direct compression method using bioadhesive polymers like Carbopol 974P, Methocel K4M and Methocel K15M in different concentrations. The modified in vitro assembly was used to measure the bioadhesive strength of tablets with fresh porcine buccal mucosa as model tissue. The tablets were evaluated for in vitro release in pH 6.8 phosphate buffer for 8 hr. The optimized formula followed non-fickian release mechanism with zero order kinetics.[42]
- 🕮 The objective of this study was to extend the GI residence time of the dosage form and control the release of rosiglitazone using mucoadhesive tablet to achieve

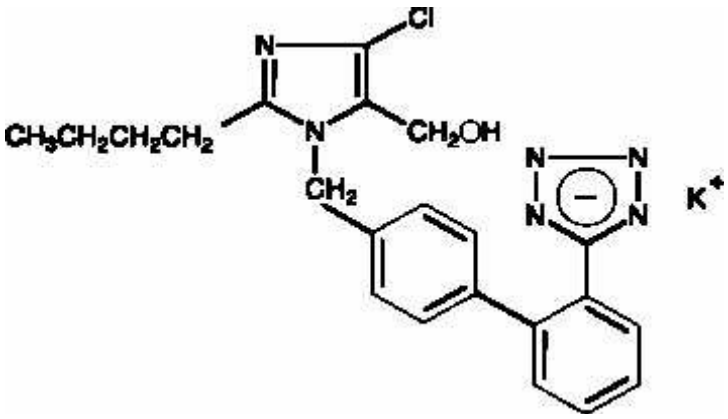
controlled plasma. Direct compression method using simplex lattice design, followed by optimization of the evaluation parameters was employed to get final optimized formulation. The optimized formulation showed a mucoadhesive strength >40 gm-f, and a mucoadhesion time >12 hours with release profile closer to the target release profile and followed Non-Fickian diffusion mediated release of rosiglitazone maleate.[43]

4. MATERIALS AND METHODOLOGY

DRUG PROFILE

LOSARTAN POTASSIUM[45, 46]

Structural formula



Chemical formula:

2 - butyl - 4 - chloro - 1 - [*p*- (*o* - 1 *H* - tetrazol - 5 - ylphenyl) benzyl] imidazole – 5 - methanol

Empirical formula: C22H22ClKN6O

Molecular weight: 461.01

Description: White or almost white powder.

Melting point: 105-110^{o}

Solubility: It is freely soluble in water and soluble in alcohols.

Half life: 2.1 hr

Drug category: anti hypertensive

Mechanism of action: Losartan potassium is an angiotensin II receptor antagonist. It suppresses the effects of angitensin II at its receptors, thereby blocking the renninangiotensin system.The rennin-angiotensin system plays a crucial role in the control of blood pressure, and in particular it is felt to play crucial role in hypertension. Losartan has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, selectively, and tolerability.

Pharmacokinetics:

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Dose: 25, 50 and 100mg.

Nervous system disorders:

Common: dizziness, vertigo

Uncommon: somnolence, headache, sleep disorders

Cardiac disorder:

Uncommon: palpitations, angina pectoris.

Vascular disorders:

Uncommon: symptomatic hypotension (especially in patients with intravascular volume

depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

Gastrointestinal disorders:

Uncommon: abdominal pain, obstipation

General disorders and administration site conditions:

Uncommon: asthenia, fatigue, oedema

Marketed Brands: LOSAR, COZAAR

POLYMER PROFILE

LOCUST BEAN GUM[47,]

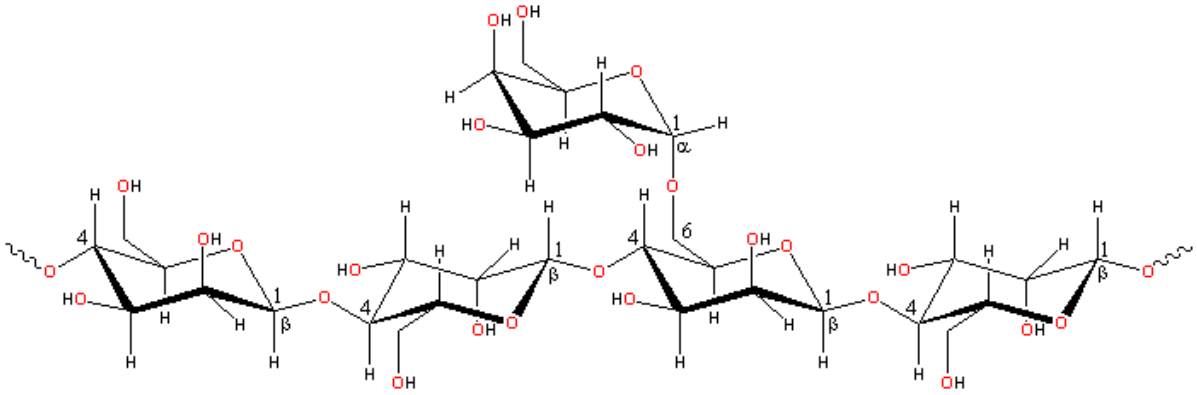
Synonyms : Algaroba; carob bean gum; carob flour; ceratonia gum; ceratonia siliqua; ceratonia siliqua gum; Cheshire gum; E410; gomme de caroube; locust bean gum; Meyprofleur; St. John's bread.

Chemical Name: Carob gum.

Empirical Formula and Molecular Weight: Ceratonia is a naturally occurring plant material that consists chiefly of a high molecular weight hydrocolloidal polysaccharide,

composed of D-galactose and D-mannose units combined through glycosidic linkages, which may be described chemically as galactomannan. The molecular weight is approximately 310 000.

Molecular Structure:



Functional Category: Controlled-release vehicle; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Ceratonia is widely used as a binder, thickening agent, and stabilizing agent in the cosmetics and food industry. In foods, 0.15–0.75% is used. Therapeutically, ceratonia mucilage is used orally in adults and children to regulate intestinal Function. Ceratonia has also been used as a tablet binder and is used in oral controlled-release drug delivery systems approved in Europe and the USA.

Description: Ceratonia occurs as a yellow-green or white colored powder. Although odorless and tasteless in the dry powder form, ceratonia acquires a leguminous taste when boiled in water.

Viscosity (dynamic): 1200–2500 mPa s (1200–2500 cP) for a 1% w/v aqueous dispersion at 258C. Viscosity is unaffected by pH within the range pH 3–11. Viscosity is increased by heating: if heated to 958C then cooled, practically clear solutions may be obtained that are more viscous than prior to heating.

Stability and Storage Conditions : The bulk material should be stored in a well-closed container in a cool, dry place. Ceratonia loses not more than 15% of its weight on drying.

Incompatibilities:

The viscosity of xanthan gum solutions is increased in the presence of ceratonia. This interaction is used synergistically in controlled-release drug delivery systems.

HYDROXYPROPYLMETHYLCELLULOSE K4M:[47]

Non-proprietary names:

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

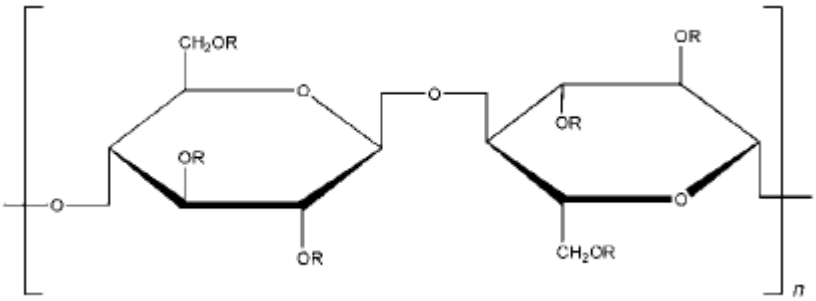
PhEur: Hypromellosum

USP: Hypromellose

Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

STRUCTURAL FORMULA



Where R is H, CH3, or CH3CH(OH)CH2

Chemical Name and CAS Registry Number

Cellulose hydroxypropyl methyl ether [9004-65-3]

Molecular weight

Approximately 10 000 –1 5,00 000.

Description

Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder.

Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent

Melting point: browns at 190–200^{0}C; chars at 225–2308C.

Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and chloromethane, and mixtures of water and alcohol

pH = 5.5–8.0 for a 1% w/w aqueous solution

Viscosity: 4000 mPa.

Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Safety

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

MAGNESIUM STEARATE[47]

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

Synonyms

Magnesium octa decanoate; octa decanoic acid, magnesium salt; stearic acid, magnesium salt.

Structural Formula

[CH3(CH2)16COO]2Mg

Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

Molecular Weight: 591.34.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional Category

Tablet and capsule lubricant

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams

Melting range:

117–1508C (commercial samples); 126–1308C (high purity magnesium stearate).

Solubility:

practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Stability and Storage Conditions

Magnesium stearate is stable and should be stored in a wellclosed container in a cool, dry place.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

TALC[47]

Nonproprietary Names

BP: Purified talc

JP: Talc

PhEur: Talcum

USP: Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name and CAS Registry Number

Talc [14807-96-6]

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Functional Category

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water.

Safety

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs.(16–18) Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants

ETHYL CELLULOSE[47]

Synonyms: Aquacoat ECD, Aqualon E 462, Ethocel

Chemical name: Cellulose ethyl ether

Molecular weight: Ranges from 0.98 × 105 to 4.10 × 105

Functional category:

Coating agent, flavoring fixative, tablet binder, tablet filler, viscosity-increasing agent.

Application in pharmaceutical formulation or technology:

It is widely used in oral and topical pharmaceutical formulation. Ethyl cellulose coatings are used to modify the release of a drug, to mask the unpleasant taste, or to improve the stability of a formulation.

Description:

It is a tasteless, free- flowing, white to light tan colored powder

Solubility:

It is practically insoluble in glycerin, propylene glycol and water. It is freely soluble in chloroform, ethanol, ethyl acetate, methanol and toluene.

Stability and storage condition:

It is a stable, slightly hygroscopic material. It should be stored at a temperature not exceeding 32 °C in a dry area.

Specific gravity: 1.12- 1.15 g/cm3

Safety: It is not recommended for parenteral products; it may be harmful to kidneys.

5. RESULTS

5.1 Preformulation Studies:

5.1.1 Organoleptic Properties:

a) Colour: A small quantity of Losartan potassium powder was taken in butter paper and viewed in well-illuminated place.

b) Taste and odour: Very less quantity of Losartan potassium was used to get taste with the help of tongue as well as smelled to get the odour.

Test	Specification/limits	Observations
Colour	White	White
Taste	Bitter	Bitter
Odour	Odourless	Odourless

Table 7: Organoleptic Properties for Losartan potassium

5.1.2. Standard plot of Losartan potassium in methanol:

Si no.	Concentration (µg/ml)	Absorbance Mean± SD
0	0	0
1	4	0.144 ± 0.026
2	8	0.262 ± 0.010
3	12	0.405 ± 0.045
4	16	0.506 ± 0.045
5	20	0.628 ± 0.055

All values are mean ± SD, n =3.

Table 8: Standard graph data of Losartan potassium in methanol at 234 nm

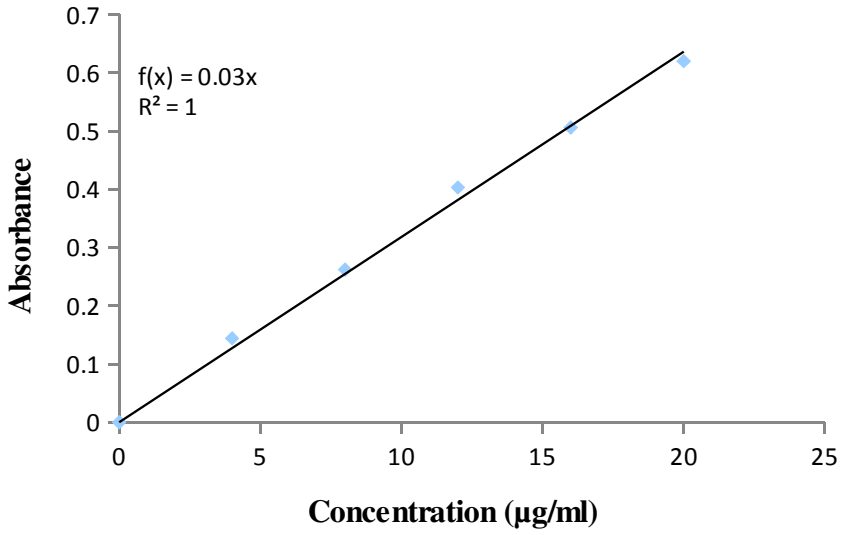


Figure 5: Standard graph of Losartan potassium in methanol

5.1.3. Fourier Transform Infrared spectroscopy:

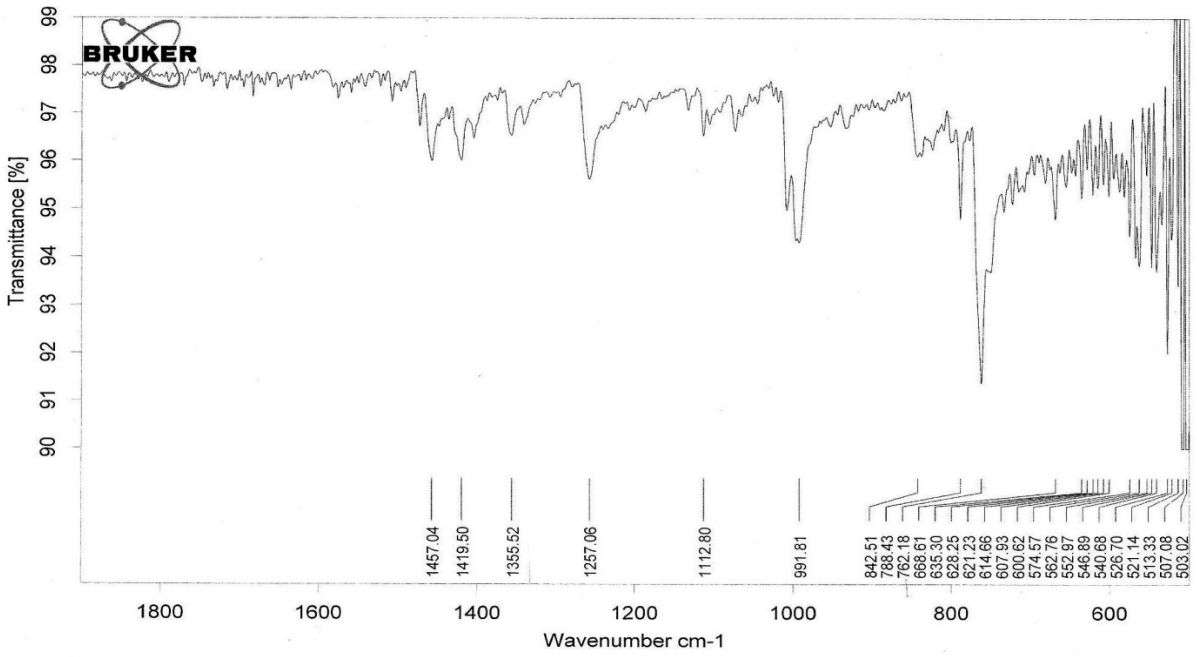


Figure 6: FT-IR Spectra of Losartan potassium

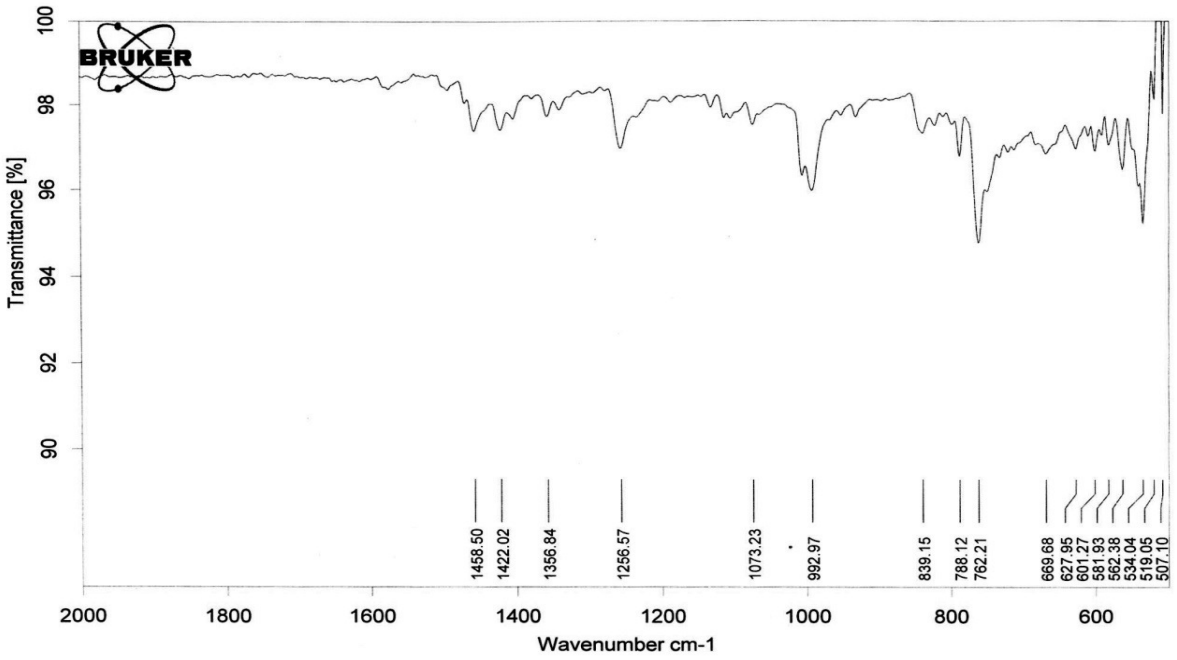


Figure 7: FT-IR spectra of Losartan potassium+ locustbean gum.

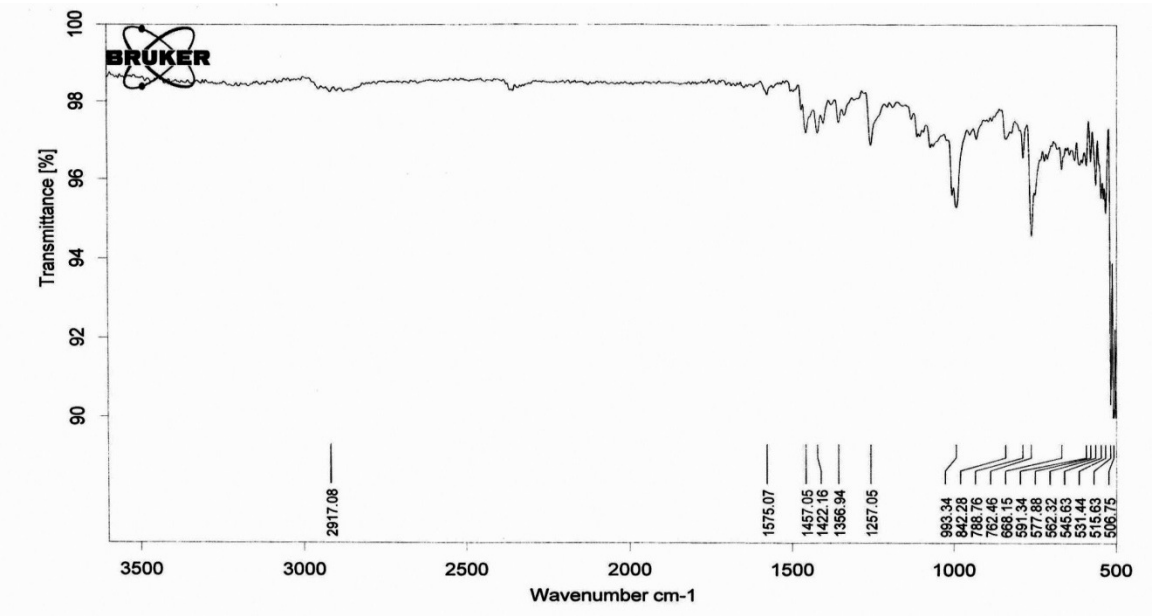


Figure 8: FT-IR spectra of Losartan potassium+ HPMC K4M

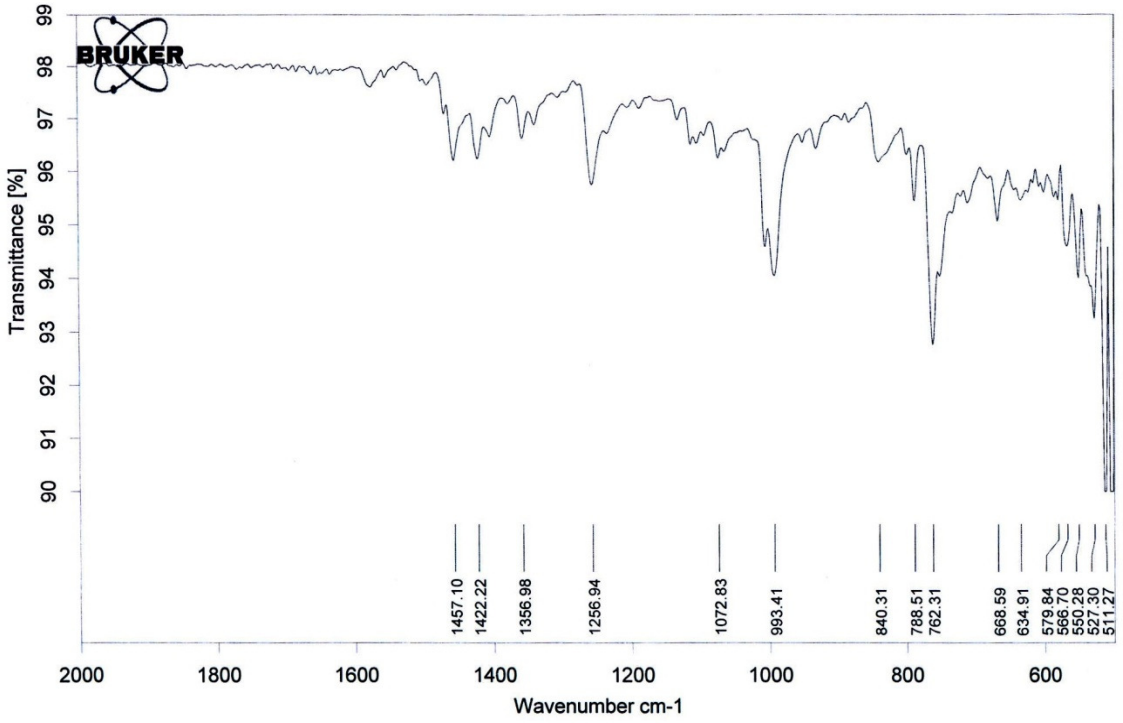


Figure 9: FT-IR spectra of Losartan potassium+ Locustbean gum+ HPMC K4M

Pure losartan potassium		
Functional group	Range	Observed range in pure drug
OH	1270-1160	1257.06
1,4 di substituted phenyl ring	850-800	842.51
1,6 substituted phenyl ring	780-720	788.43
C-Cl	850-550	668.61
C-C arometic	1500-1400	1457.04
NH	910-665	762.31

Table 9: FTIR Spectral data of Losartan potassium

Name of pure drug	Standard value of drug(cm^{-1})	Observed value of LOCUSTBEAN GUM with drug(cm^{-1})	Observed value of KPMC K4M with drug(cm^{-1})	Observed value of polymer combination with drug(cm^{-1})
	1160 -1270	1256.57	1257.05	1256.94
	800-850	839.15	842.28	840.31
	720-780	788.12	788.76	788.51

Losartan potassium	550-850	669.68	668.15	668.59
	1500-1400	1458.50	1457.07	1457.10
	910-665	762.21	762.46	762.31

Table 10: interpretation for IR spectra of Losartan potassium and polymers

5.1.4 Differential Scanning Calorimetry (DSC):

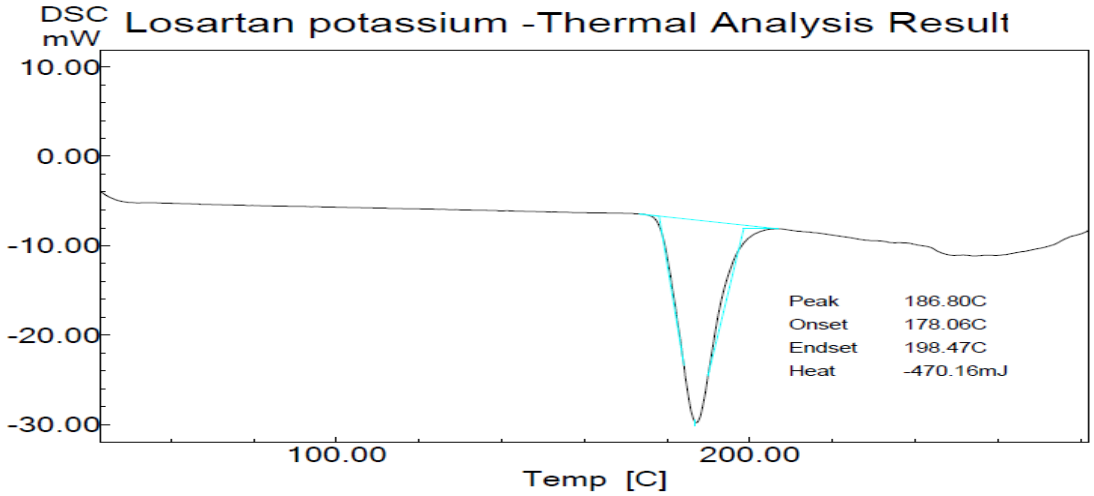


Figure 10: DSC of losatran potassium

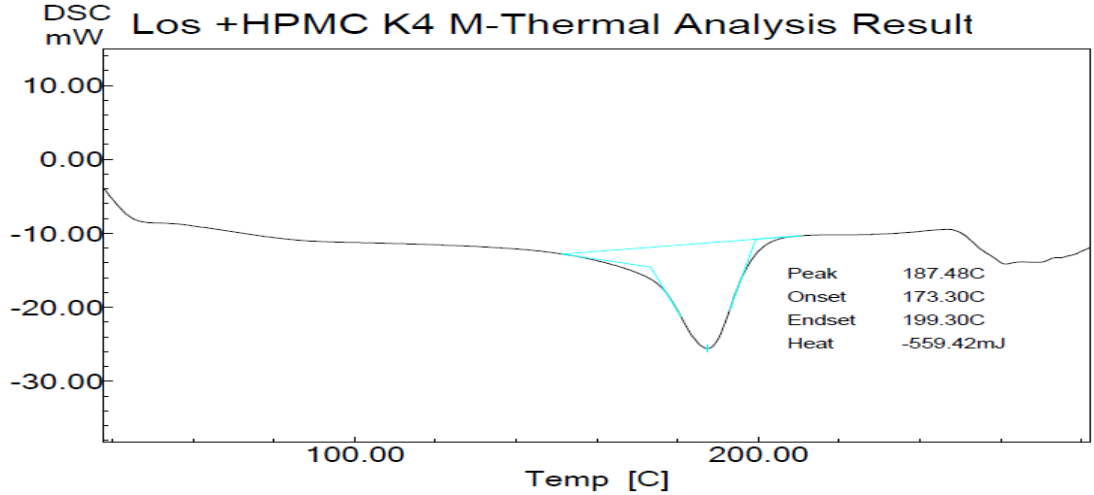


Figure 11: DSC of losartan potassium and HPMC K4M

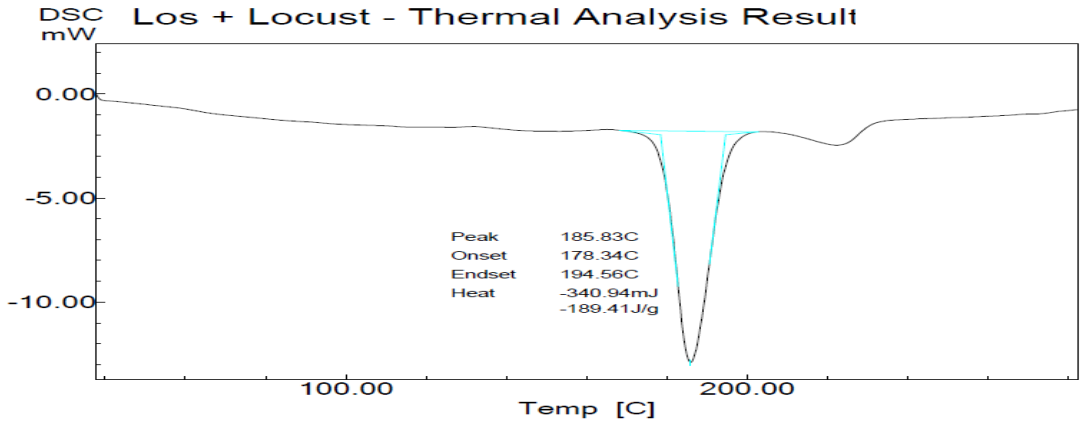


Figure 12: DSC of losartan potassium+ locust bean gum

5.2. Precompression parameters for Losartan potassium

5.2.1. Bulk density, tapped density and compressibility index:

BATCH CODE	BULK DENSIY (GM/CM^3)	TAPPED DENSITY (GM/CM^3)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO	ANGLE OF REPOSE (Θ)
F1	0.443	0.544	18.6	1.23	31.1
F2	0.457	0.552	17.4	1.21	28.5
F3	0.443	0.539	17.9	1.22	29.1
F4	0.453	0.541	16.28	1.19	29.88
F5	0.459	0.538	14.8	1.18	26.8
F6	0.422	0.549	21.4	1.27	31.6

F7	0.459	0.559	17.8	1.22	30.52
F8	0.433	0.513	15.4	1.18	29.62
F9	0.437	0.526	16.76	1.21	28.6

Table 11: Data of bulk density, tapped density, compressibility index, Hauser's ratio and angle of repose.

5.2.2. Evaluation of buccal tablets

A. Physicochemical parameters

Formulation	Hardness kg/cm2	Thickness (mm)	Weight Variation (mg)	Friability (% loss)
F1	3.1 ± 0.42	3.8 ± 0.28	194.2 ± 0.81	0.51 ± 0.27
F2	5.0 ± 0.18	4.2 ± 0.04	235.9 ± 1.62	0.31 ± 0.06
F3	4.2 ± 0.09	4.1 ± 0.15	234.8 ± 0.77	0.29 ± 0.24
F4	7.8 ± 0.26	4.8 ± 0.91	285.3 ± 4.26	0.11 ± 0.43
F5	3.2 ± 0.84	4.0 ± 0.52	209.8 ± 0.98	0.38 ± 0.37
F6	6.0 ± 0.12	4.5 ± 0.22	268.1 ± 1.45	0.25 ± 0.08
F7	3.5 ± 1.53	3.9 ± 0.08	203.9 ± 3.11	0.42 ± 0.09
F8	6.5 ± 2.41	4.6 ± 0.05	274.2 ± 2.81	0.22 ± 0.18
F9	6.0 ± 0.35	4.2 ± 0.51	239.6 ± 1.86	0.28 ± 0.24

All values are mean ± SD, n =3.

Table 12: Physicochemical parameters of developed buccal tablets

B. Drug Content uniformity:

Formulation	Amount of drug present (mg)	% Drug content
F1	98.45±0.061	98.45±0.061
F2	98.06±0.031	98.06±0.031
F3	97.10±0.026	97.10±0.026
F4	98.84±0.035	98.84±0.035
F5	99.29±0.025	99.29±0.025
F6	97.42±0.025	97.42±0.025
F7	96.45±0.035	96.45±0.035
F8	97.29±0.042	97.29±0.042
F9	98.71±0.028	98.71±0.028

All values are mean ± SD, n =3.

Table 13: Amount of drug present and % drug content

C. % Swelling index of the developed buccal tablets

% SWELLING INDEX					
Formulation	2h	4h	6h	8h	10h
F1	56	69	75	88	102
F2	85.4	98	110	120	142
F3	78.3	90.2	99	115	120.6
F4	85.2	114.5	125.8	134.4	151
F5	73.7	90	95.6	105	114.6
F6	82	106	118	136	149
F7	61.4	81.5	91.6	100.6	112
F8	57.4	84.4	87	98	121
F9	82.4	103	112	123	144

Table 14: % Swelling index of developed formulations

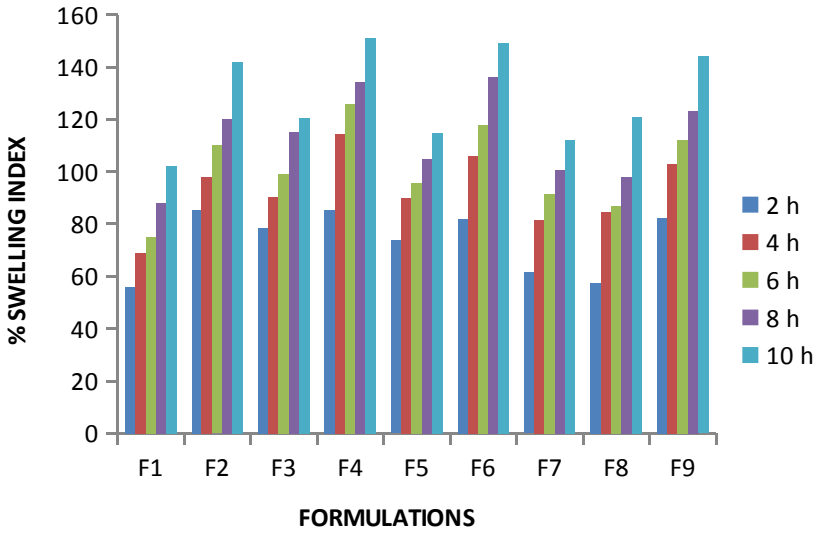


Figure 13: % swelling index graph of 9 formulations

D. Bioadhesive properties

Formulation	mucoadhesive time (h)	Bioadhesion strength (gm)	Force of adhesion (N)	Surface pH
F1	8.4	20.6 ± 0.05	0.202 ± 0.24	5.6 ± 0.04
F2	>10	30.2 ± 0.24	0.296 ± 0.66	6.1 ± 0.42
F3	9.2	21.6 ± 0.11	0.211 ± 0.047	6.8 ± 0.09
F4	>10	29.1 ± 0.42	0.285 ± 0.52	7.0 ± 0.06
F5	7.2	18.9 ± 0.08	0.185 ± 0.051	5.8 ± 0.52
F6	>10	31.5 ± 0.14	0.309 ± 0.81	6.4 ± 0.08
F7	9.45	25.4 ± 0.37	0.249 ±0.62	5.6 ± 0.05
F8	>10	27.1 ± 0.19	0.266 ± 0.06	6.8 ± 0.11
F9	>10	26.5 ± 0.66	0.259 ± 0.14	6.2 ± 0.22

All values are mean ± SD, n =3.

Table 15: Bioadhesive properties of developed buccal tablets

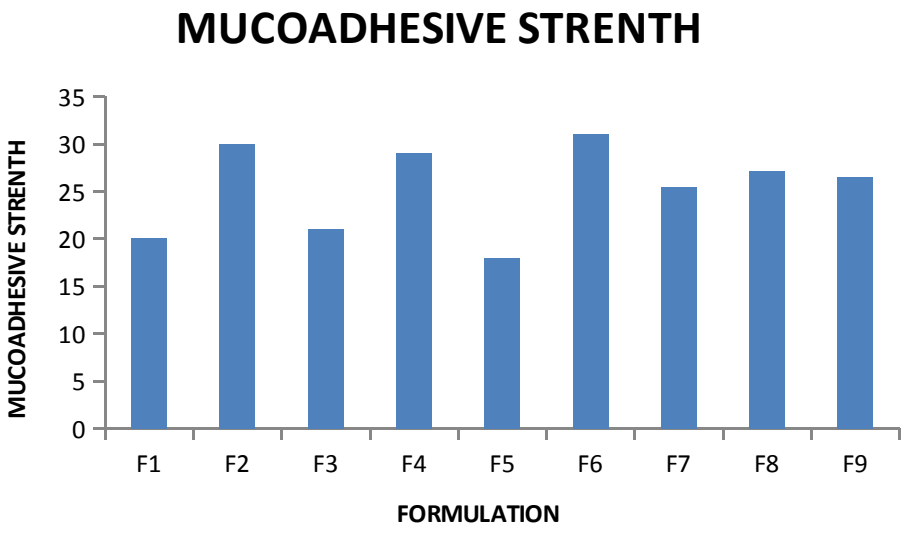


Figure 14: Mucoadhesive strenth of developed buccal tablets

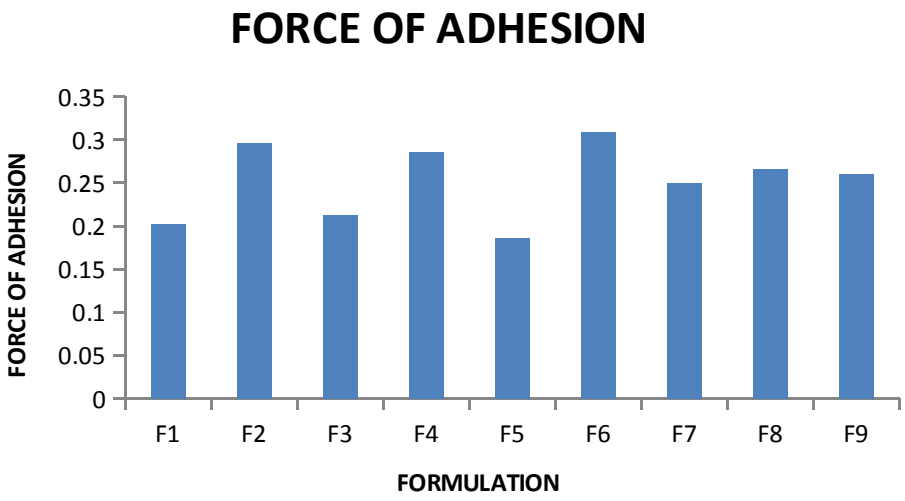


Figure 15: Force of adhesion of developed buccal tablets

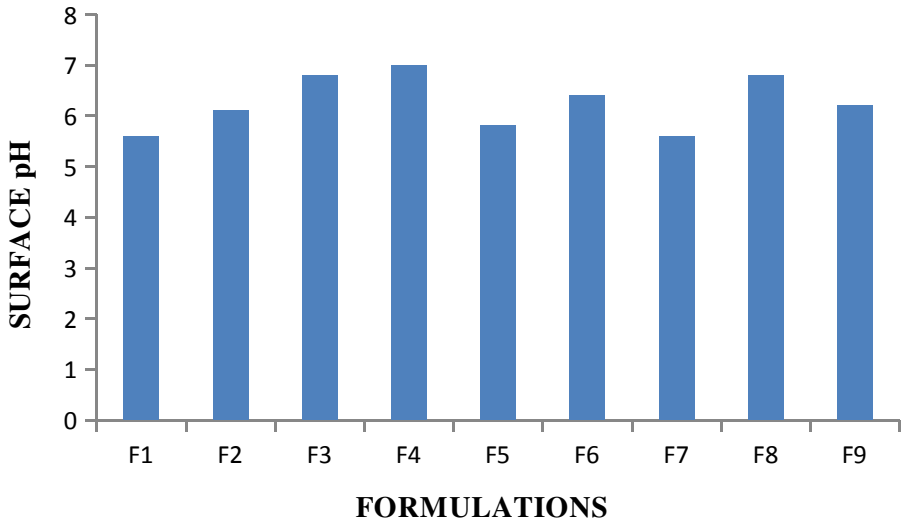


Figure 16: Surface pH of 9 formulations

E. *In-vitro* dissolution studies.

Time (h)	% Cumulative Drug Release		
	F1	F2	F3
0	0	0	0
0.5	25.25±0.08	21.48±0.055	23.22±0.065
1	35.26±0.15	25.96±0.065	34.38±0.124
2	46.49±0.06	31.91±0.082	42.71±0.092
3	60.69±0.11	35.57±0.124	49.91±0.11
4	69.15±0.14	43.89±0.154	58.02±0.064
5	77.39±0.04	52.84±0.086	66.18±0.082
6	86.21±0.16	58.07±0.064	72.63±0.035
7	93.06±0.12	62.74±0.063	79.42±0.0258
8	96.47±0.076	72.37±0162	85.37±0.124
9		87.57±0.115	89.31±0.16
10		94.42±0.214	93.28±0.066

All values are mean ± SD, n =3

Table 16: *In-vitro* drug release data for formulations F1 - F3

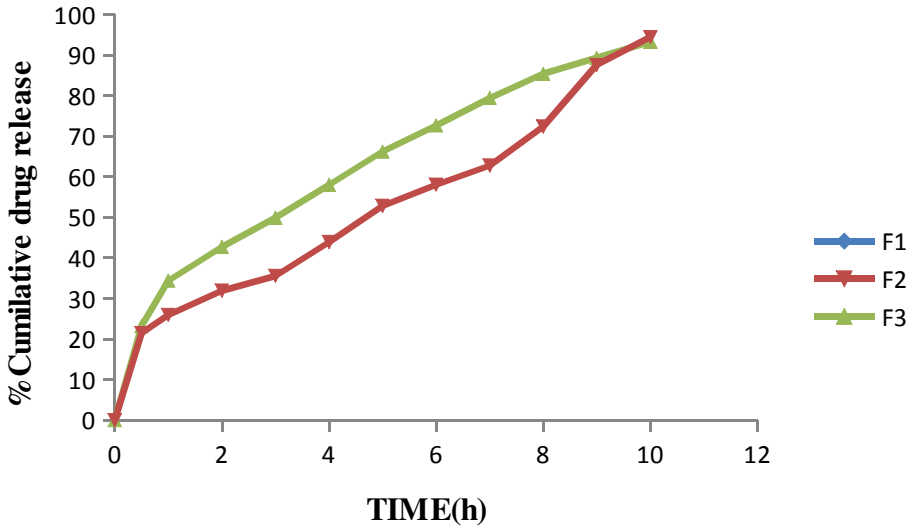


Figure 17: % CDR of Formulations F1-F3

Table 17: *In-vitro* drug release data for formulations F4 – F6

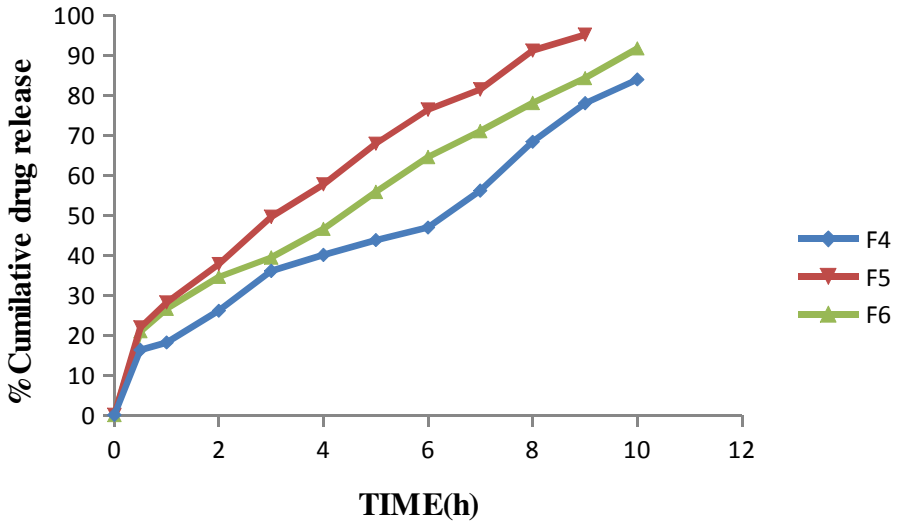


Figure 18: % CDR of Formulations F4-F6

Time (h)	% Cumulative Drug Release		
	F7	F8	F9
0	0	0	0
0.5	22.06±0.24	18±0.061	20.91±0.042
1	30.32±0.051	23.06±0.025	26.07±0.38
2	40.94±0.24	27.23±0.038	33.36±0.25
3	47.55±0.25	34.64±0.15	40.51±0.16
4	55.65±0.55	40.92±0.42	45.08±0.035
5	68.15±0.081	47.53±0.091	53.46±0.061
6	79.55±0.12	54.47±0.12	58.69±0.028
7	87.82±0.18	60.86±0.062	69.46±0.25
8	95.56±0.62	70.19±0.034	77.090±0.062
9		77.54±0.024	85.35±0.13
10		87.83±0.062	95.97±0.095

All values are mean ± SD, n =3

Table 18: *In-vitro* drug release data for formulations F7 – F9

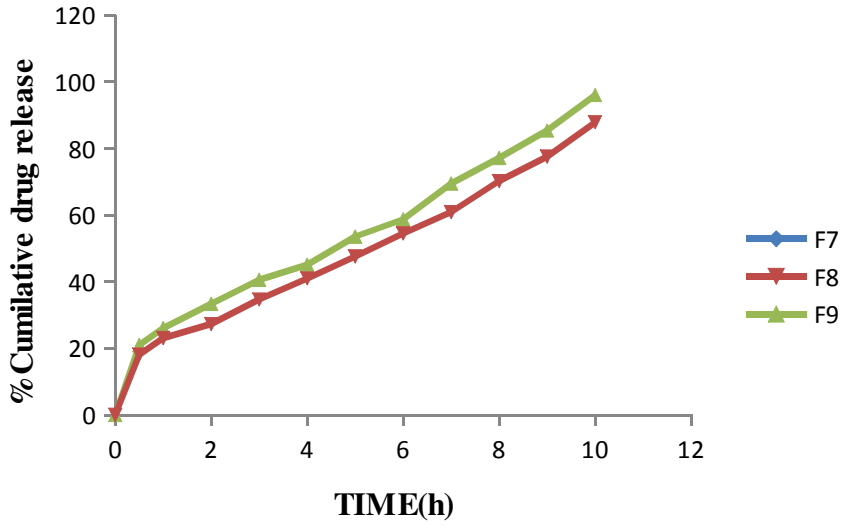


Figure 19: % CDR of Formulations F7-F9

Figure 20: Comparison of zero order of in vitro drug release F1-F4

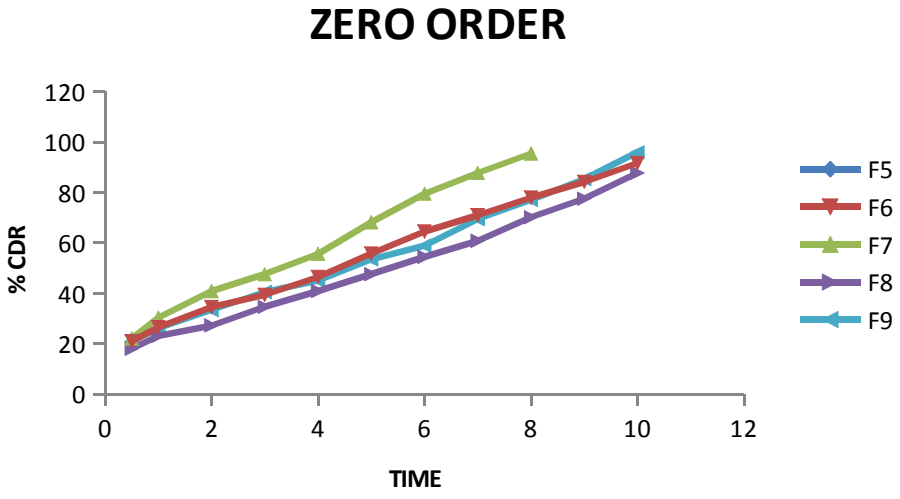


Figure 21: comparison of zero order of in vitro drug release F5-F9

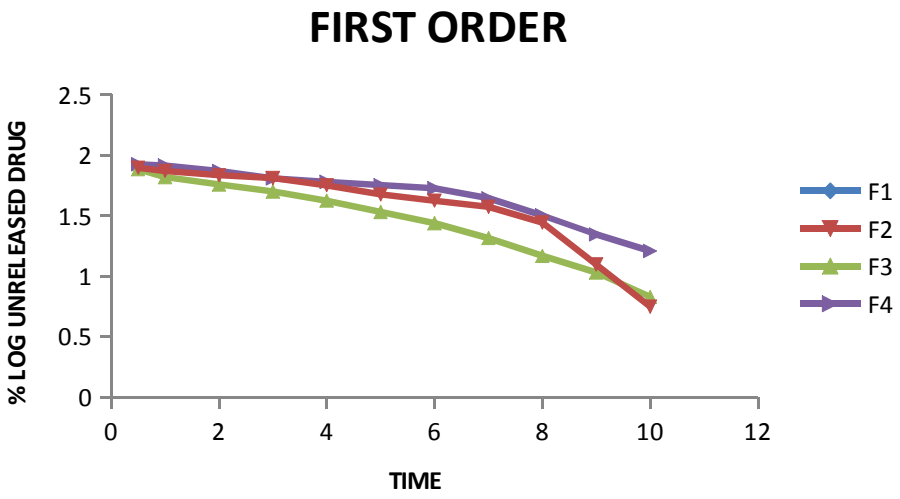


Figure 22: comparison of first order of in vitro drug release F1-F4

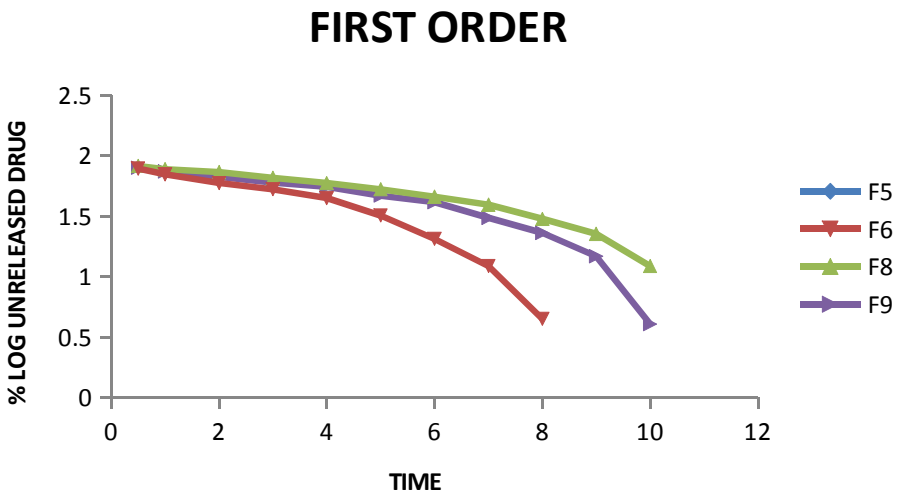


Figure 23: comparison of first order of in vitro drug release F5-F9

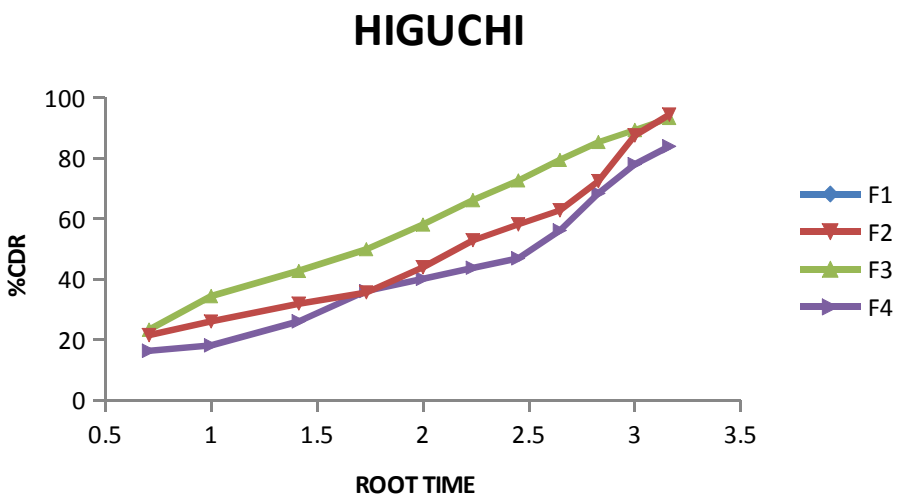


Figure 24: comparison of Higuchi model of in vitro drug release F1-F4

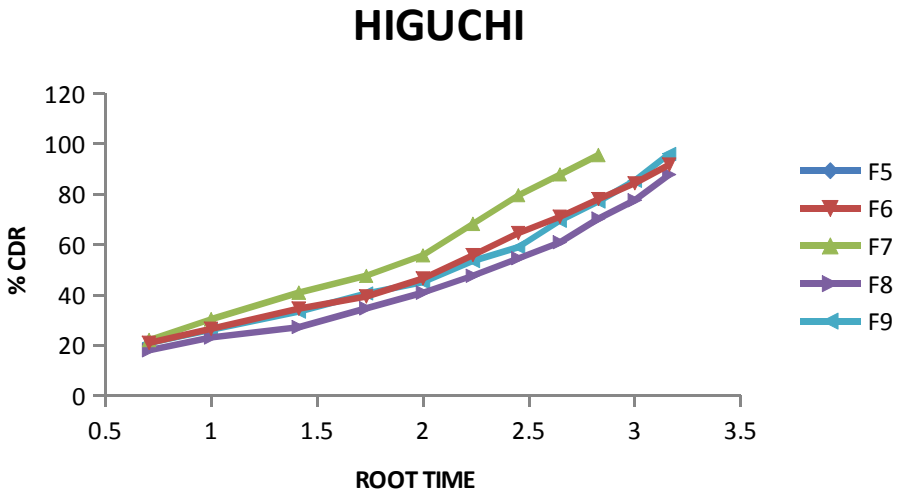


Figure 25: comparison of Higuchi model of in vitro drug release F5-F9

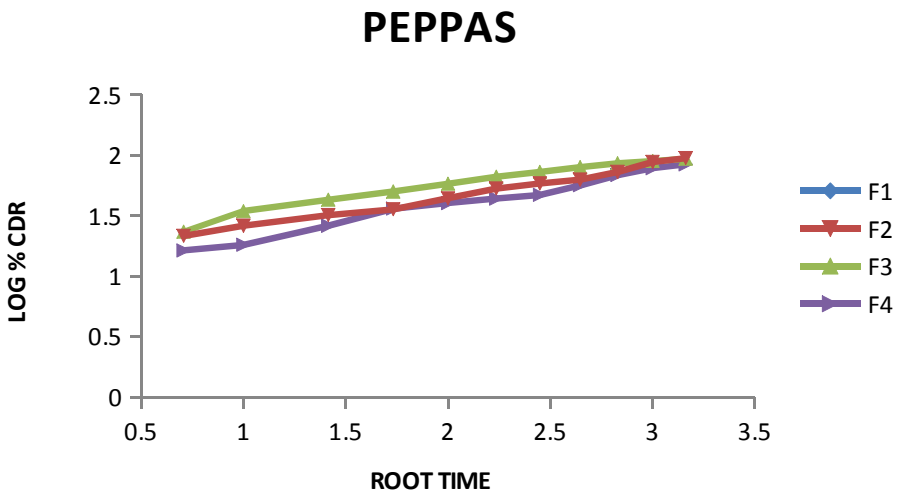


Figure 26: comparison of Korsmeyers-peppas equation of in vitro drug release F1-F4

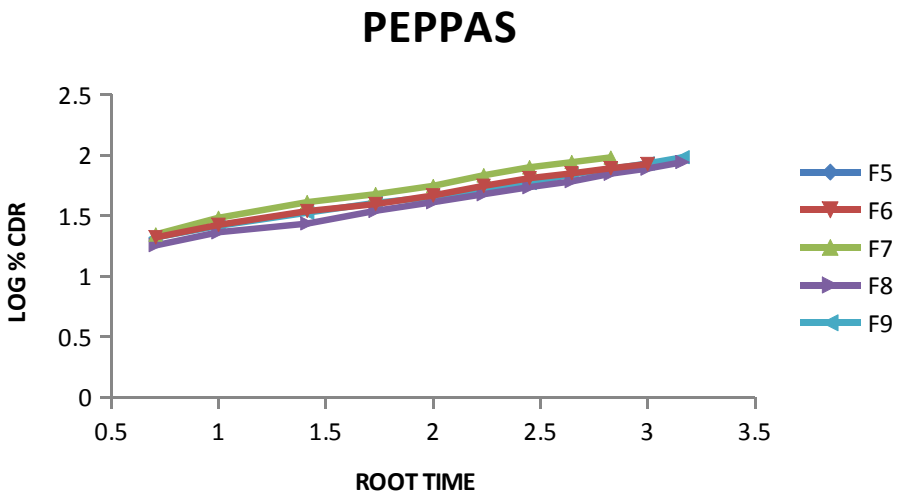


Figure 27: comparison of Korsmeyers-peppas equation of in vitro drug release F5-F9

5.3. OPTIMIZATION

The runs or formulations, which are designed based on central composite design, are evaluated for the response. The response values are subjected to multiple regression analysis to find out the relationship between the factors used and the response values obtained. The response values subjected for this analysis are;

1. Percentage of Drug Release at 1st hour
2. Percentage of Drug Release at 8st hour.
3. n value
4. Mucoadhesive strength
5. Hardness

The duration of above responses were chosen for the analysis of the following relationship:

1. To study the effect of amount of Locustbean gum
2. To study the effect of amount of HPMC K4M.
3. To study the combined effect of Locustbean gum, HPMC K4 M.

The multiple regression analysis was done using design expert 8.0.4.1 software, which is specially meant for this optimization process. The results of this analysis are presented in the table 20.

Using the regression coefficient of the factors, the polynomial equation for the response is constructed. Only significantly, contributing factors are considered for the equation generation.

Run	Locustbean gum	HPMC K4M	%CDR at 1st h	%CDR at 8th h	n value	Mucoadhesive strenth gm/cm^2	hardnes gm/cm^2
1	18.00	20.00	35.27	97.93	0.495	20	3.1
2	60.00	20.00	25.96	72.37	0.49	30	5
3	18.00	70.00	34.39	85.37	0.452	21	4
4	60.00	70.00	18.09	68.32	0.56	29	8
5	9.30	45.00	28.11	91.14	0.529	18	3.2
6	68.70	45.00	26.54	78.03	0.501	31	6
7	39.00	9.64	30.32	97.59	0.527	25.4	3
8	39.00	80.36	23.06	70.19	0.525	27.1	6.5
9	39.00	45.00	26.07	77.09	0.502	26.5	6

Table 20: Design and Summary Response Data

Response 1: % cumulative drugrelease at 1st houre

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	142.02	2	71.01	4.86	0.0557
A	96.82	1	96.82	6.62	0.0422
B	45.21	1	45.21	3.09	0.1292
Residual	87.74	6	14.62	-	-
Cor Total	229.76	8	-	-	-

Table 21: ANOVA for Response Surface Linear Model

Factor	Coefficient	STANDARD DF

	Estimate	
A-locust bean gum	-3.48	1
B-hpmc k4m	-2.38	1

Table 22: Estimated regression coefficient

Final Equation in Terms of Coded Factors:

DRUG RELEASE AT 1 h= +27.53- 3.48* A-2.38* B

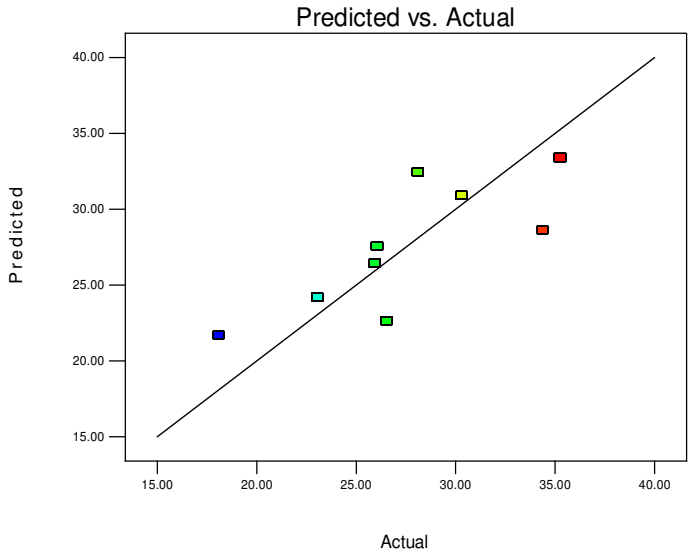


Figure 28: Correlation between actual and predicted values for drug release at 1 h (R1)

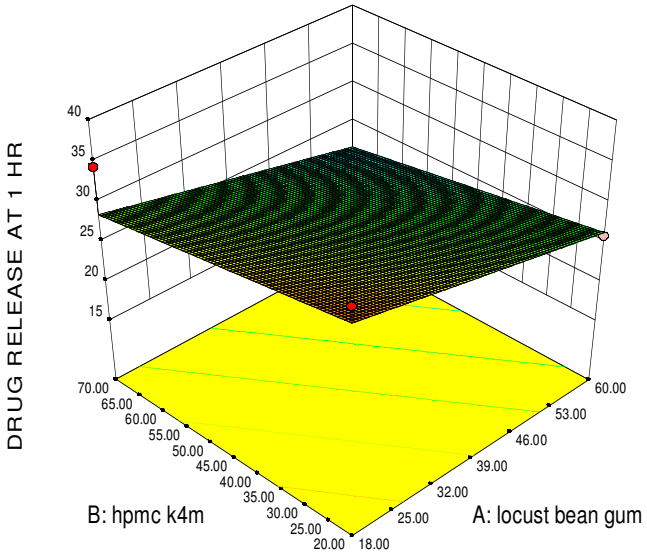


Figure 29: 3-D graph showing effect of Locustbean gum and HPMC K4M on drug release at 1 h (R1)

Response 2: % cumulative drug release at 8 th houre

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	850.50	2	425.25	12.73	0.0069
A	467.42	1	467.42	13.99	0.0096
B	383.08	1	383.08	11.47	0.0147
Residual	200.43	6	33.40	-	-
Cor Total	1050.93	8	-	-	-

Table 23: ANOVA for Response Surface Linear Model

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	-7.64	1

B-hpmc k4m	-6.92	1

Table 24: Estimated regression coefficient

Final Equation in Terms of Coded Factors:

DRUG RELEASE AT 8 h = +82.00-7.64 * A-6.92* B

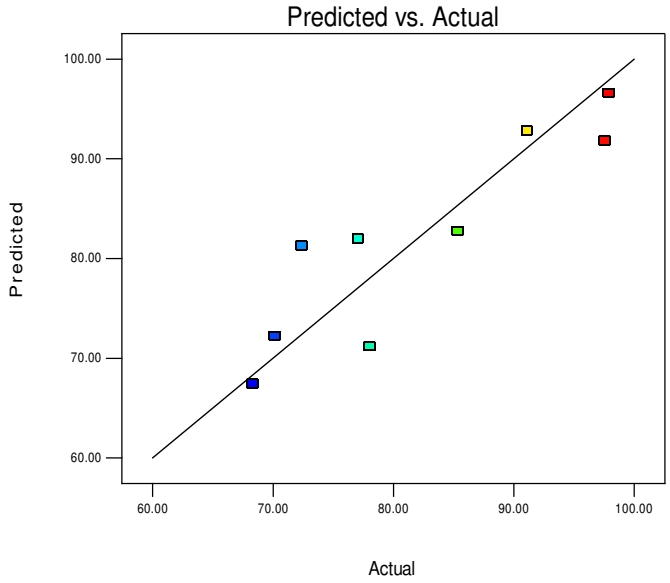


Figure 30: Correlation between actual and predicted values for drug release at 8 h (R2)

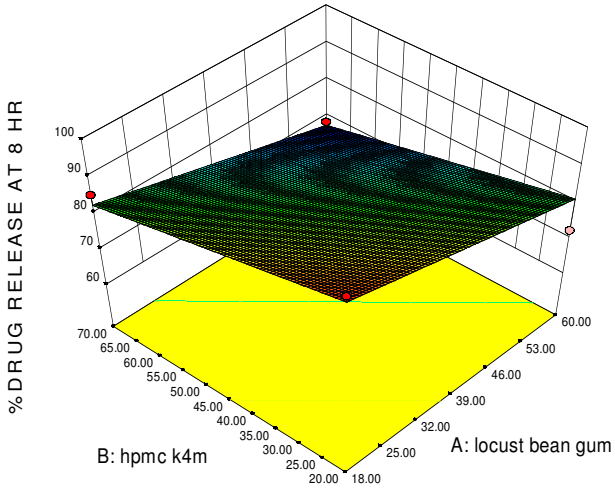


Figure 31: 3-D graph showing effect of Locustbean gum and HPMC K4M on drug release at 8 h (R2)

Response 3: n value

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	3.768E-003	3	1.256E-003	1.68	0.2848
A	5.025E-004	1	5.025E-004	0.67	0.4493
B	7.303E-005	1	7.303E-005	0.098	0.7671
AB^3	3.192E-003	1	3.192E-003	4.28	0.0935
Residual	3.732E-003	5	7.464E-004	-	-
Cor Total	7.500E-003	8	-	-	-

Table 25: ANOVA for Response Surface 2FI Model

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	7.925E-003	1
B-hpmc k4m	3.021E-003	1
AB	0.028	1

Table 26: Estimated regression coefficient

Final Equation in Terms of Coded Factors:

n value: +0.51+7.925E-003 * A +3.021E-003 * B+0.028* A * B

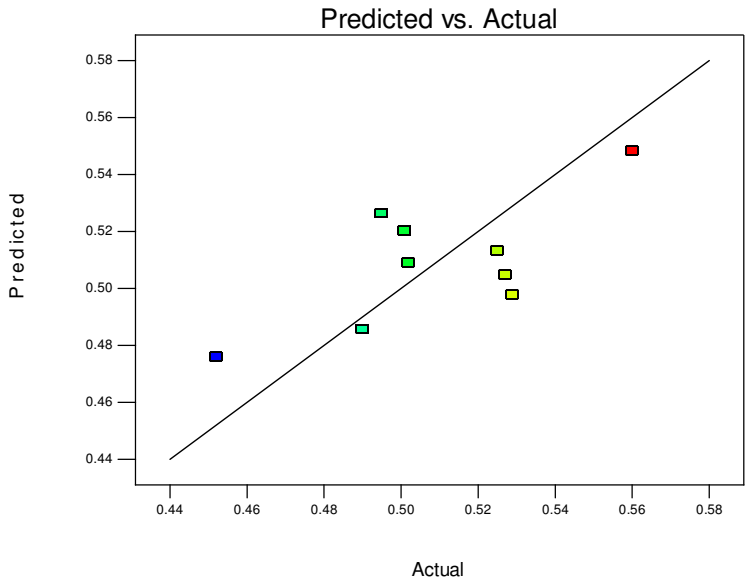


Figure 32: Correlation between actual and predicted values for n value (R3)

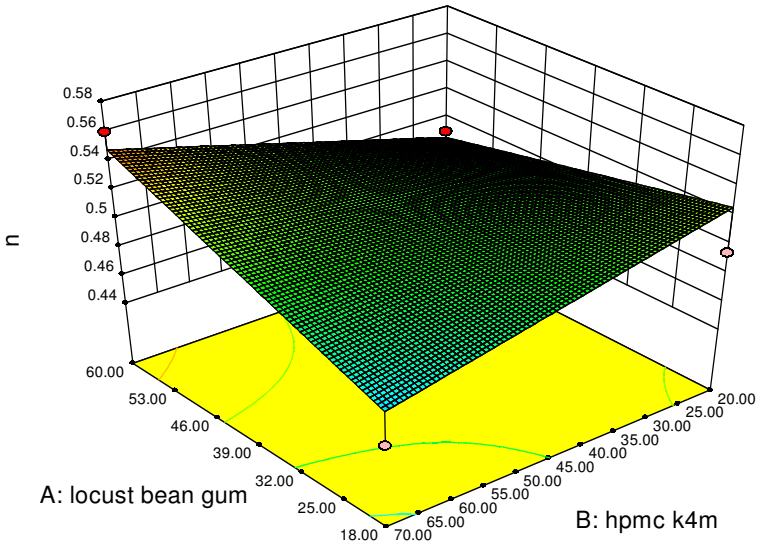


Figure 33: 3-D graph showing effect of Locustbean gum and HPMC K4M on n value (R3)

Response 4: Mucoadhesive strength

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	166.20	2	83.10	75.36	< 0.0001
A	165.48	1	165.48	150.07	< 0.0001
B	0.72	1	0.72	0.66	0.4492
Residual	6.62	6	1.10		
Cor Total	172.82	8			

Table 27: ANOVA for Response Surface Linear Model

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	4.55	1
B-hpmc k4m	0.30	1

Table 28: estimated regression coefficient

Final Equation in Terms of Coded Factors:

Mucoadhesive strenth = +25.33+ 4.55 *A+0.30 * B

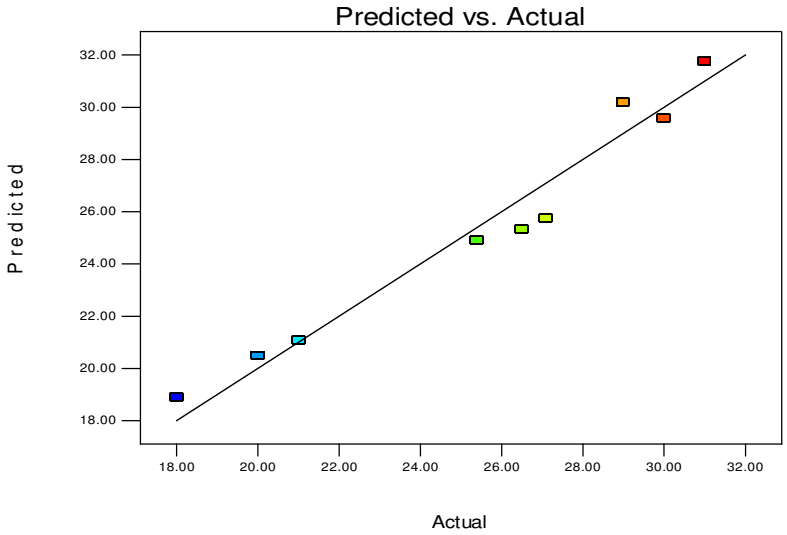


Figure 34: Correlation between actual and predicted values for Mucoadhesive strenth (R4)

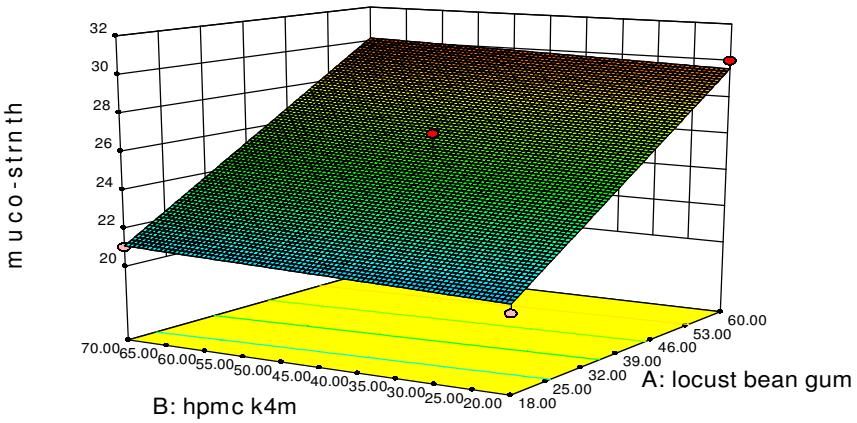


Figure 35: 3-D graph showing effect of Locustbean gum and HPMC K4M on mucoadhesive strenth (R4)

Response 5: hardness

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	21.94	2	10.97	20.87	0.0020

A	12.15	1	12.15	23.12	0.0030
B	9.79	1	9.79	18.62	0.0050
Residual	3.15	6	0.53	-	-
Cor Total	25.10	8	-	-	-

Table 29: ANOVA for Response Surface Linear Model

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	1.23	1
B-hpmc k4m	1.11	1

Table 30: Estimated regression coefficient

Final Equation in Terms of Coded Factors:

hardness = +4.98+1.23 * A+1.11 * B

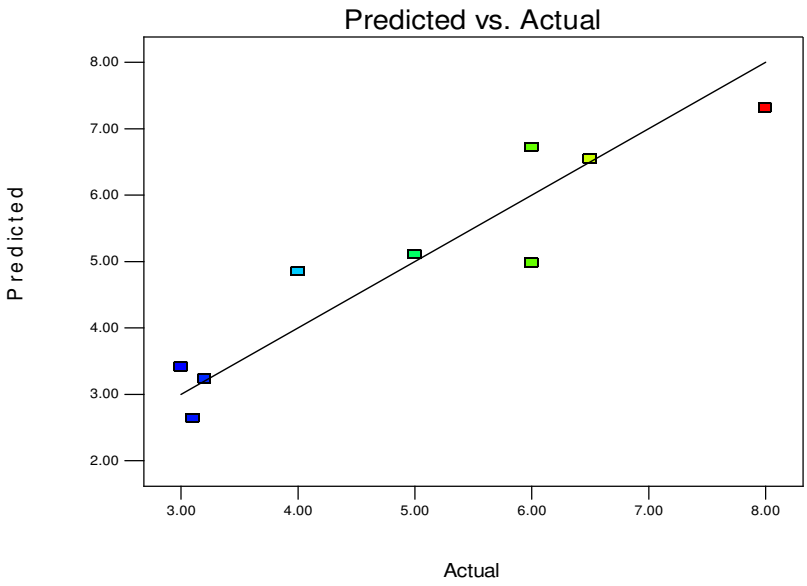


Figure 36: Correlation between actual and predicted values for hardness (R5)

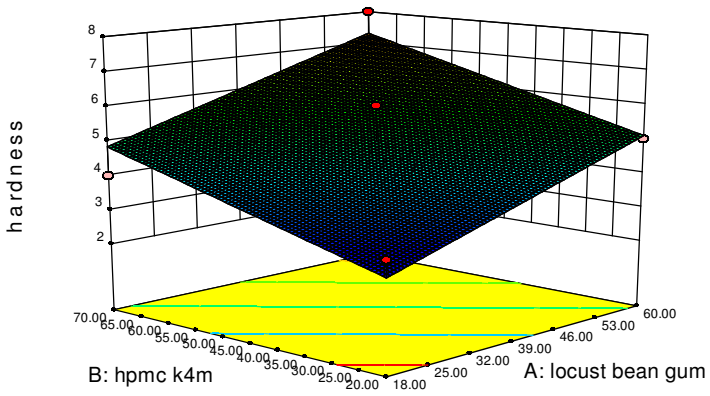


Figure 37: 3-D graph showing effect of Locustbean gum and HPMC K4M on hardness (R5)

5.3.1. Optimized formula

*INGREDIENTS	R
Losartan potassium	100
Locustbean gum	46.59
HPMC K4M	55.45
Mannitol	15

Magnesium stearate	5
Talc	3
Aerosil	2
Ethyl cellulose	30
TOTAL	257.04

Table 31: Composition of the optimized formula.

5.3.2. Comparison between the experimental (E) and predicted (P) values

Optimized Formulation	Dependable Variables				
	% CDR at 1h	% CDR at 8h	n	Mucoadhesive strength g/cm^2	Hardness Kg/cm^2
Predicted	25.27	76.35	0.52	27.11	5.89
Experiment	25.08	77.2	0.521	27	5.9

Table 32: Comparison between the experimental (E) and predicted (P) values for the most probable optimal formulation

5.3.3. Results for optimization batch

Sr. No.	Parameters	Results
1.	Appearance	Good
2.	Hardness	5.9 kg/cm^2
3.	Friability	0.21
4.	Drug content	99.03 %
5.	Ex- vivo mucoadhesion strength	27 g/cm^2
6.	Ex- vivo mucoadhesion time	10.50 h
7.	Surface pH	6.2
8.	% Swelling index at 10 h	145.4
9.	In- vitro drug release	97.30

Table 33: Results for optimization batch

Drug release kinetic studies for optimized formula

Zero order

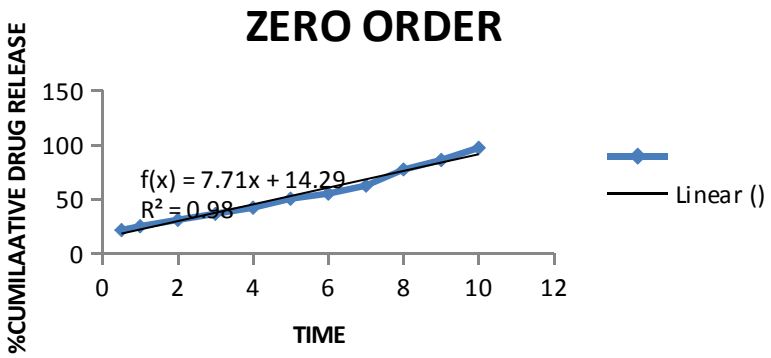


Figure 38: zero order of invitro release for optimized formula

First order

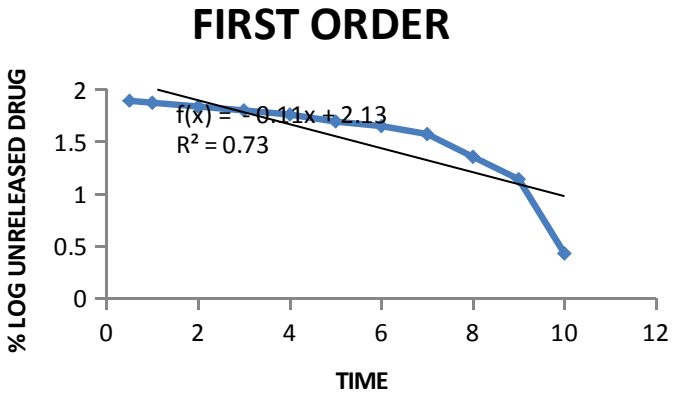


Figure 39: First order of invitro release for optimized formula

Higulachi

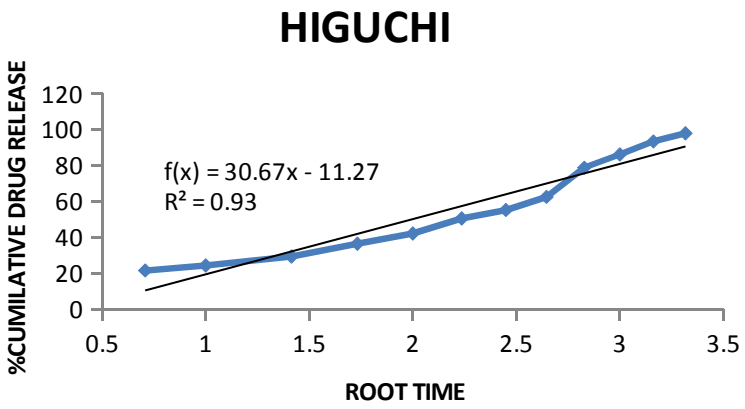


Figure 40: Higuchi of invitro release for optimized formula

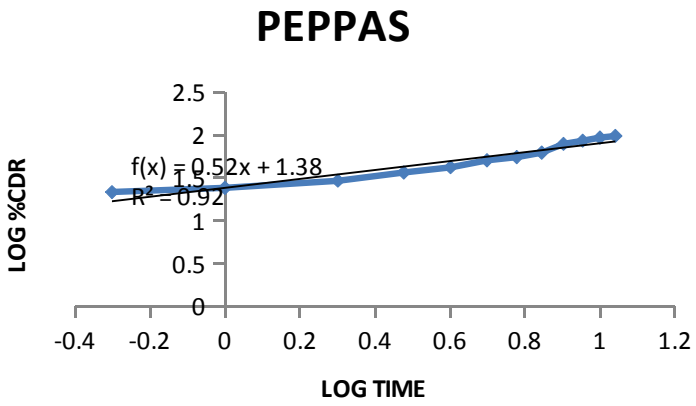


Figure 41: Korsmeyers-peppas equation of in vitro drug release for optimized formula

5.4: Stability studies

Time	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% CDR at 10 h	Mucoadhesive strength
Initial	5.91±0.22	0.21±0.42	99.03±0.62	97.30±0.61	27±0.12
First Month	5.9±0.82	0.22±0.52	99.0±0.12	97.12±0.0.26	27.4±0.44
Second Month	5.94±0.24	0.20±1.6	99.12±0.22	97.4±0.34	27.28±0.32
Third Month	5.86±0.912	0.212±0.88	98.92±1.05	97.06±0.24	27.06±1.0

Table 34: At ambient condition (25±2°C and relative humidity 60± 5%)

Time	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% CDR at 10 h	Mucoadhesive strength
Initial	5.91±0.32	0.21±0.08	99.03±0.21	97.31±0.15	27.2±0.21
First Month	5.92±0.24	0.218±0.42	99.0±0.21	97.42±0.08	27.18±0.21
Second Month	5.932±0.22	0.208±0.105	99.12±1.1	97.28±0.12	27.6±0.18
Third Month	5.892±0.16	0.212±0.21	99.1±0.52	97.08±0.11	27.11±1.02

Table 35: At elevated temperature (40±2°C and relative humidity 75± 5%)

6. DISCUSSION

Mucoadhesive buccal drug delivery system is a promising tool for the drugs with low oral bioavailability due to extensive first pass effect and also this route provides an easy termination of drug effect and it avoids the first pass metabolism. Losartan potassium is the first orally active angeotensin II receptor antagonist with low oral bioavailability due to extensive first pass metabolism.

In the present work, mucoadhesive buccal tablets of losartan potassium were prepared by using locust bean gum with HPMC K4M by direct compression method.

6.1 Preformulation studies:

6.1.1. Identification:

The Losartan potassium was estimated using methanol solution and the calibration curve was constructed in this solution at 243 nm as shown in table-8, figure-5. The method obeys Beer-Lambert‘s law in the studied range of 4-20 mcg/ml with high r^2 value of >0.996 and low SD value suggested that method was reproducible and hence suitable for estimation of losartan potassium.

6.1.2. FTIR Study:

Pure drug losartan potassium exhibited characteristics absorption bands which given in table 9, the IR regions mentioned below:

The peak 1457.04 cm^{-1} may be due to C=C aromatic ring stretching 1257.06 cm^{-1} may be due to OH bending 842.51 cm^{-1} may be due to1,4 di substituted phenyl ring 788.43 cm^{-1}

may be due to 1,6 substituted phenyl ring 668.61 cm^{-1} peak due to the C-Cl group and 762.31 cm^{-1} peak due to the NH group.

The IR data of the formulation was compared with the standard spectrum of pure drug losartan potassium and the characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymeric carrier (formulation) were noted. The IR spectra of losartan potassium with combination of polymers are shown in table-10. The IR spectrum of the formulation showed that there is no significant evidence for interaction between drug and the polymer. Peaks of both drug as well as formulation were observed are same. So this clearly suggest that the drug has not undergone any interaction with the polymer in the formulation, as there is no any shift in the positions of the characteristic absorption bands of drug in the formulation.

Mucoadhesive buccal tablets of losartan potassium were prepared by direct compression method using locust bean gum in varying concentration as a primary polymer and combination with HPMC K4M in fixed amount. The optimized formulation of Losartan potassium mucoadhesive buccal tablet is presented in Table-31. The total 9 formulation are prepared and weight obtained for tablets was from 193-285 mg. the weights are shown in the table-4.

6.1.3 Differential Scanning Calorimetry (DSC):

In DSC studies melting peak appeared at 186.80^0 C for losartan potassium. There was no

change in the melting point of binary mixture of losartan potassium and HPMC K4M and

losartan potassium and locust bean gum which indicate that there is no interaction between drug and polymers.

6.2. EVALUATION PARAMETERS FOR LOSARTAN POTASSIUM:

6.2.1. Precompression parameters for Losartan potassium

In the present study, direct compression method was adopted for buccal tablets. The data's were shown in Table 11. The values for angle of repose were found in the range of 26.8° to 31.6°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.422 to 0.459 (gm/cm^3) and 0.513 to 0.559 (gm/cm^3) respectively. Carr's index of the prepared blends fall in the range of 14.8% to 21.4%. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

6.2.2. Evaluation of buccal tablets

A. Physico-chemical evaluation of tablets:

Hardness:

The hardness of prepared mucoadhesive buccal tablets was from 3.1 to 7.8 kg/cm^2 and the data's were shown in Table 12. The hardness is increased due to increasing weight of the tablet. Also the hardness of the tablet was increased as the concentration of locust bean gum and HPMC K4M were increased in each formulation.

Hardness R 5 = +4.98+1.23*A+1.11* B

The linear model is selected for this response with F-value 20.87 and p value is 0.0020 which indicates the model is significant. Both the factors A, locust bean gum and factor B, HPMC K4M increase the hardness of the buccal tablets.

Thickness, weight variation and Friability:

The average thickness of the all buccal tables ranges from 3.8 to 4.8 mm. The value of percentage variation in weight and friability were shown in the table 12. All the formulation values found to be within the limit of conventional oral tables stated in the *Indian pharmacopeia*.

B. Drug Content uniformity:

Drug content uniformity study was carried out on the tablets of every batch and the data's were shown in the Table 13. The content uniformity of all the formulations was found to be in the range of 96.45% to 99.29% which showed that there was uniform distribution of the drug throughout the batch.

C. % Swelling index at 10 h:

The swelling study of prepared buccal tablets was performed in phosphate buffer pH 6.8 and the results are presented as percentage weight change with respect to time in Table 14 and in figure 13. The swelling behaviour of a bioadhesive system is an important property for uniform and prolonged release of drug and bioadhesion. The swelling index of buccal tablets were directly proportional to the concentration of the polymer, as the polymer

concentration increases there was increase in the swelling index. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The % swelling index was found 102 to 151. The F4 and F6 shown better swelling index compare to the other formulations, which shown 151 % and 149 % these formulations contains high concentrations of locust bean gum and HPMC K4M. The locust bean gum and HPMC K4M both are increasing the swelling effect for tablets. The locust bean gum showing more swelling effect (30) compare to HPMC K4M because locust bean gum has more gelling capacity. The order of swelling of polymeric tablets were F4>F6>F9>F2>F8>F3>F5>F7>F1.

D. Bioadhesive properties

Ex vivo mucoadhesive time:

The prepared mucoadhesive buccal tablets were evaluated for *ex vivo* residence time using porcine buccal mucosa and the results are tabulated in Table 15. *Ex vivo* residence time is the time necessary for complete detachment or erosion of tablet from mucosal surface without losing integrity. This test reflects the adhesive capacity of polymer used in formulation. All the tablet formulations showed a residence time of 7.2 h to more than 10 h. As all the polymers used were hydrogel forming hydrophilic matrix and get swelled to adhere to the mucus surface. The *ex vivo* residence time relates directly to the swelling index. The polymer locust bean gum showed maximum of >10 h residence time with prolonged drug release indicates best formulation as controlled release system. As the concentration of locust bean gum increased there was significant increase in residence time.

Effect of variables on bioadhesive strength:

The mucoadhesive strength of prepared mucoadhesive buccal tablet was studied using porcine buccal mucosa and the mucoadhesive parameters are represented in Table15. Bioadhesion is generally understood to define the ability of a biological or synthetic material to “stick” to a mucous membrane, resulting in adhesion of the material to the tissue for a protracted period of time. In general, bioadhesion is considered to occur in three major stages: wetting, interpenetration, and mechanical interlocking between biological tissue and polymer. The mucoadhesive strength is affected by molecular weight of polymer, contact time with membrane and degree of swelling of the polymer· Water uptake process produces polymer swelling and improves the consolidation step that increases the mobility of molecules and facilitates that interpenetration with the biological tissue layer. So, the polymer swelling is a property related to the bioadhesion of the system the constant and regression coefficient for bioadhesive strength are as follow:

muco-strnth R4 = +25.33 + 4.55*A + 0.30* B

The Linear model is selected for this response with F - value 75.36 and P- value less than 0.0001 implies the model is significant. Figure 32 represent the observed responcse values compared to that of prdicted values for optimised formula. The effect of A and B can be further elucidated with the help of response surface plot (Fig 33). Both the factor A and B have an synergestic effect on the bioadhesive strengh. At high level of factor A gave higher value of bioadhesive strength(29) than that of factor B. If A kept high level and at all levels of B bioadhesive strength was observed higher values. As increase the concentration of factor A and B increases the bioadhesive strength. Locust bean gum

shows higher bioadhesive strength, when compare to the HPMC K4M due to high molecular weight, polymer chain flexibility for chain interpenetration and diffusion with mucin.

Surface pH:

The surface pH for all the buccal tablets was from 5.6 to 7.0 which were nearer to salivary pH 6.5-7.5 suggesting that the prepared buccal tablets can be used without the risk of mucosal irritation and discomfort.

E. In vitro drug release study after 8 hour:

The *in vitro* release of losartan potassium was performed in phosphate pH 6.8. Total amount of losartan potassium released from all formulations ranges from 68.33% to 96.47% in 8 hours Table 16, 17, 18. Decreased rate of drug release was observed with increased concentration of polymers. Figure 17, 18, 19 illustrates the release profile of all formulations. When the tablets contact with water the gel formation of polymers occurs which acts as rate controlling matrix for the release of drug molecules In this case, effect of both polymers can be explained by mathematical equation in terms of actual factors:

%DRUG RELEASE AT 8 h R2 = +82.00 -7.64 *A - 6.92 * B

The Linear model is selected for this response with Model F-value 12.73 and p value is 0.0069 indicate the model is significant. Both the factors A, locust bean gum and B, HPMC K4M decreases drug release from the tablet. The factor A has shown more nagetive effect which indicates that drug release decrease as factor increases. The locust bean gum is a natural gum it will swellin an aqueous medium to form a gel like matrix that controls release by acting as a barrier to drug dissolution and diffusion. Locust bean

gum shows the higher controlling effect on the release of drug than the HPMC K4M due to formation of higher viscous solution. The effect of A and B can be further elucidated with help of response surface plot figure 31. At high level of factor A lower value of drug release and at all levels of factor B the release was decreased which indicates factor A has more significant negative effect.

In vitro drug release study after 1 hour:

Total amount of losartan potassium released from all formulations ranges from 23.06% to 35.26 % in 1 hour table 16, 17, 18. Decreased rate of drug release was observed with increased concentration of polymers. Fig 17, 18, 19 illustrates the release profile of all formulations. Effect of both polymers can be explained by mathematical equation in terms of actual factors:

DRUG RELEASE AT 1h R1 = +27.53 - 3.48 *A - 2.38 *B

The Linear model is selected for this response with Model F-value 4.86 and p value is 0.0557 indicate the model is significant. Both the factors A, locust bean gum and B, HPMC K4M decreases drug release from the tablet. The factor A has shown more nagetive effect which indicates that drug release decrease as factor increases. factor A Locust bean gum shows the higher controlling effect on the release of drug than the HPMC K4M due to formation of higher viscous solution. The effect of A and B factors can be explained by using of response surface plot (Figure 29). At high level of factor A gave lower value of drug release at all level of factor B which indicates factor A has significant nagetive effect.

F. Kinetics of drug release:

The drug release data was fitted into the different models like Korsmeyer Peppas, zero order and Higuchi eqation shown very close and above 0.9 r^2 values (table 19). It suggests that the release of drug from the formulations may follow any one of these models. The r^2 values of zero order of all the formulations have shown higher value which indicate the drug release is directly propertional to the time. But n values range from 0.458 to 0.562 which indicate Fickian diffusion mechanism. According to Higuchi model, the drug release from matrix is dirctly propertional to square root of time and explains the Fickian diffusion. However, n values of Korsmeyer-Peppas strongly indicates that diffusion mechanism is Fickian.

G. Effect of formulation variable on release exponent:

The 2FI Model was found to be not significant for drug release kinetics with the model F-valu 1.68 and p value 0.2848 In this response, factor A and B was found to be not significant. So, the model equation is as follows:

n value R3 = +0.51+7.925E-003* A + 3.021E-003* B + 0.028 * A * B

In this response, both the factors have positive effect. The effect of factor A and B can be explained with help of the response surface plot (Fig 33). As the concentration of the polymer A and B increase the n value increases. The n value of optimized formula found to be 0.521 which indicates the mechanism of release is Fickian. The factor A with higher concentration shows the higher effect on value of the release exponent(n) than the factor B. At high level of factor A gave high value of n at all level of factor B which indicates that factor A has significant effect.

ANOVA, pure error, lack of fit

The result of ANOVA demostrate that the model was singnificant for all dependent variables (Table 20). Regression analysis was carried out to determine the regression coefficients. All the independent variables (Factors) were found to be significant for all R1, R2, R4, R5, response variables. The linear model were found significant for R2,R4,R5. So, above result indicate that both the factors play an important role in the formulation of buccal tablet containing losartan potassium.

6.3. Optimization:

In the numerical optimization techniques, the desirability approch was used to generate the optimum settings for the formulation. For the optimized formulation, the drug release at 1st hour was kept at maximize, the drug release at 8 hour was kept at minimize, bioadhesive strength, hardness were kept at maximize, release exponent (n) was kept in the range. The composition of optimized formula is losartan potassium (100 mg), locust bean gum (46.59 mg) and HPMC K4M (55.45 mg). The optimized formulation was prepared according to predicted model and evaluted for responses. A good releationship between the experimental and predicted values (table 32), which confirms the precticability and validity of the model.

6.4. Stability Study:

The stability studies were carried out for the optimized formula at 40 ± 2^{o}C/75 ± 5% RH for three months. Table 35 shows the values of post-compressional parameters after stability studies at different temperature and humidity conditions. The results indicated that the tablets did not show any physical changes (hardness, colour and friability) during

the study period and the drug content was found above 98.92% at the end of 3rd month. This indicates that tablets are fairly stable at storage condition.

CONCLUSION:

The study performed on "formulation and evaluation of mucoadhesive buccal tablets of losartan potassium" reveals following conclusion:

The mucoadhesive buccal tablets of losartan potassium could be prepared using locustbean gum and HPMC K4M by direct compression method.

The IR spectra revealed that, there was no interaction between polymers and drug. All polymers used were compatible with drug.

All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification.

The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation.

All the buccal tablets showed good residence time of 7.2 H to >10 h, indicated good adhesive capacity of polymers used.

The CCD was used to find out the effect of independent varibles on the dependable variables. The result of CCD revealed that the locustbean gum and HPMC K4M have significant effect on the mucoadhesion strenth, swelling index, the drug release at 1 h and

the drug release at 8 h. The observed independent variables were found to be very close to predicted values of optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of buccal tablet containing losartan potassium by using locustbean gum and HPMC K4M. The drug release form the optimized formula was found to be following the zero order kinetics and n value range of the Peppas equation is 0.521, which indicates fickian diffusion mechanism. Thus the release of drug from the dosage form was found to be time dependent.

The stability studies revealed that there was no significant change in buccal tablet properties with aging at different storage conditions.

Hence, the mucoadhesive buccal tablets of losartan potassium can be prepared with enhanced bioavailability and prolonged therapeutic effect for the better management of hyper tension.

SUMMARY

- The losartan potassium is an angeotensin II receptor antagonist which is used in treatment of hypertension disorder. The aim of this work was to develop a mucoadhesive buccal tablet for the buccal delivery of the losartan potassium via buccal mucosa.
- Total 9 formulations of losartan potassium mucoadhesive buccal tablets are designed to release drug at mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. Locustbean gum and HPMC K4M were selected as mucoadhesive polymer.
- UV Spectroscopic method was used for the determination of losartan potassium in methonol at 234 nm.
- The results of the drug–excipient compatibility FT-IR, DSC studies revealed that there was no chemical interaction between the pure drug and excipients.
- The tablets were prepared by direct compressiom method. 9 formulations were designed by using central composite design using different concentrations of locustbean gum and HPMC K4M.
- The prepared formulations were evaluated for the precompression parameters such as angle of repose, bulk density, and % compressibility. All the parameters were found to be within the limits.
- The post compression parameters such as weight variation, thickness, hardness, friability, drug content, swelling index, surface pH, bioadhesive properties such as bioadhesive time, bioadhesive strength, and *In-vitro* dissolution.

- From the data obtained, it is observed that Amongst the various combinations of the polymers used in the study, the buccal tablets were formulated by direct compression method using locustbean gum (39 mg) and HPMC K4M (45 mg) exhibited better results than compared to those other combination of polymers in different concentration. The effectiveness of polymers (locustbean gum and HPMC K4M) on the drug release was explained.
- The Central composite design was utilized using different concentrations of polymers, locustbean gum (A), HPMC K 4M (B) were selected as independent variables. The drug release at 1^{st} h (R1), drug release at 8 h (R2), release exponent n value (R3), mucoadhesive strength (R4) and hardness (R5) were select as dependent variables. A total of 9 formulations was obtained and optimized. The developed optimized formulation was further challenged with experimentation and was found that, the predicted values were in close agreement with the actual values, indicating the validation of the model.
- The stability studies were carried out for the optimisation formulation and that showed no major change in physicho chemical parameters, mucoadhesive strength, swelling index, drug content, and *In-vitro* dissolution profile.
- Hence, based on the above study it was concluded that in-situ gel of controlled release Metformin Hydrochloride can be successfully developed on a lab scale.

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